CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210872Orig1s000

CLINICAL REVIEW(S)

Clinical Review
Edward H. Chin, MD, MPH
NDA 210872
ZuraPrep, Isopropyl Alcohol 70% v/v

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	210872
Priority or Standard	Standard
Submit Date(s)	6/29/2018
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PDUFA Goal Date	4/28/2019
Division/Office	DNDP
Reviewer Name(s)	Edward H. Chin, MD, MPH
Review Completion Date	2/28/2019 (Draft)
Established/Proper Name	Isopropyl alcohol 70% v/v
(Proposed) Trade Name	ZuraGard™
Applicant	Zurex Pharma, Inc.
Dosage Form(s)	Solution
Applicant Proposed Dosing Regimen(s)	• Remove applicator from package; do not touch sponge. • Hold applicator down. Depress the end cap/button to release the antisepetic, solution will flow into sponge. • (b) (4), completely wet the treatment area • Dry surgical sites (such as abdomen or arm): use repeated back-forth strokes (b) (4) for (b) (4) 30 seconds. • Moist surgical sites (such as inguinal fold): use repeated back-forth strokes (b) (4) for (b) (4) 2 minutes • Allow solution (b) (4) completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair). Do not blot or wipe away. • Discard the applicator after single use along with any portion of the solution which is not required to cover the prep area. It is not necessary to use the entire amount available.
Applicant Proposed Indication(s)/Population(s)	Preoperative skin preparation solution for use in presurgical settings as an antiseptic/antimicrobial agent to reduce bacteria that potentially can cause skin infection. Use with care in premature infants or infants 2 months of age.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as proposed indication.

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
ATE	average treatment effect
BLA	biologics license application
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
CSS	Controlled Substance Staff
DFL	Drug Facts Label
DMEPA	Division of Medication Error Prevention and Analysis
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
GCP	good clinical practice
IND	Investigational New Drug Application
IPA	Isopropyl Alcohol
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
MB	Methylene Blue
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OSI	Office of Scientific Investigation
OTC	Over the Counter
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy

RLD	Reference Listed Drug
SAE	serious adverse event
SAP	statistical analysis plan
SSI	Surgical Site Infection
TEAE	treatment emergent adverse event
TFM	Tentative Final Monograph

1. Executive Summary

1.1. Product Introduction

Zurex Pharma, Inc. submitted NDA 210872 for ZuraPrep™ (IPA 70%) on June 29, 2018. ZuraPrep™ is a single-use, topical antiseptic/antimicrobial agent for use in presurgical settings to reduce the bacteria that can contribute to healthcare associated infections such as SSIs. ZuraPrep does not contain any NMEs. The components of the ZuraPrep™ formulation include (b) (4) IPA, citric acid (b) (4), (b) (4) (b) (4) methylparaben, propylparaben, MB (b) (4), and purified water. IPA was demonstrated to be the only active ingredient. The to-be-marketed dosage form comprises a single-use 10.5-mL plastic applicator containing ZuraPrep™ solution with a sterile barrier system to ensure that the applicator surfaces are sterile. The solution is applied topically to the patient using back and forth strokes of the sponge for approximately 30 seconds on dry surgical sites and approximately 2 minutes on moist surgical sites. The solution is allowed to completely dry for a minimum of 3 minutes on dry, hairless sites or up to 1 hour in hair. To highlight the coverage area once applied to the skin, the ZuraPrep™ formulation includes an excipient (b) (4) MB (b) (4). This NDA is a 505(b)(2) submission, relying upon the FDA's findings of safety for ChloraPrep® (NDA 020832) as both contain the IPA 70% v/v and have the same dosage form, route of administration, and indication for use. Please note that FDA label review done by DMEPA concluded that the proposed proprietary name was not acceptable (b) (4) (b) (4) The sponsor responded by changing the proprietary name to ZuraGard™. ZuraGard™ is recognized as the newly approved proprietary name, but as previously submitted supportive documents use the proprietary name ZuraPrep™, this review will continue to use ZuraPrep™ to avoid confusion.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Zurex Pharma, Inc. has demonstrated that ZuraPrep™ meets criteria for safety and efficacy as per the criteria outlined in applicable TFMs, Final Rules and other FDA guidance. Zurex demonstrated that ZuraPrep™ is effective in reducing the required amount of bacteria in the required time frame after topical application on dry intact skin without significant safety concerns or signals. Pivotal studies were not designed to measure the effects of ZuraPrep™ use on rates of SSIs or other healthcare associated infections, but effective skin antisepsis is essential in preventing or reducing the incidence of healthcare-associated infections occurring with surgical procedures.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

SSIs remain a substantial cause of morbidity, prolonged hospitalization, and death. Causes are multifactorial but bacteria from surgical sites are often the source of infection. Prevention of hospital associated infections, including SSIs, requires multiple preventive measures at multiple phases of the surgical process. The FDA does not require a reduction in rates of SSIs for approval of ZuraPrep™ or other similar alcohol based antiseptic products. Efficacy and effectiveness for ZuraPrep™ is determined in terms of the responder rates of study subjects as determined by quantifiable reductions in bacteria on dry intact skin after application on healthy adults. Skin preparation with alcohol based antiseptics as a preventive measure for hospital associated infections is recognized by the CDC as a Category IA recommendation, making it a strong recommendation supported by high quality evidence.

The submitted safety studies focused on the risk of adverse skin reactions that might be expected with topical application of ZuraPrep™. The studies were appropriately conducted and did not identify any unexpected skin reactions or safety signals. AEs reported from the safety population were low in number and acuity. Examples of AEs potentially related to ZuraPrep™ included rash, irritation, and folliculitis, but these AEs were low in number and resolved. The safety profile overall matched or exceeded the safety profile of the RLD (ChloraPrep®) used in the studies. No safety issues or signals were identified that would preclude approval of ZuraPrep™.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In US, over 16,000 SSIs reported following nearly 850,000 operative procedures for an overall rate of 1.9% between 2006-2008. • In 2014, estimates of SSI incidence rates ranged from 2%-5%. • Mortality of 3% associated with SSIs • 75% of SSI-associated deaths being directly attributable to the SSI • Cost of SSI treatment in US estimated at $3.5-$10 billion annually.	SSIs remain a substantial cause of morbidity, mortality and prolonged hospitalization after surgical procedures. Causes are multifactorial but bacteria from surgical sites are often the source of infection. Insufficient antisepsis would contribute to SSIs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Prehospital: preoperative bathing, smoking cessation, glucose control, MRSA screening, bowel preparations • Hospital: glucose control, hair removal, proper skin preparation, antibiotic prophylaxis, wound protection, antibiotic sutures, topical antibiotics, wound care • Intraoperative skin preparation with an alcohol-based antiseptic agent. Other IPA antiseptic agents combined with other active ingredients (chlorhexidine, provodine iodine) with IPA.	Prevention of hospital associated infections and SSIs requires multiple preventive measures at multiple phases of the surgical process. Use of alcohol-based antiseptic agents is recognized as an important preventive measure.
Benefit	• At 10 minutes post-application, ZuraPrep™ achieved a 70% responder rate, considered therapeutically effective in 2 pivotal efficacy studies (ZX-ZP-0073, ZX-ZP-0074) • Responder status based on response per body area at 10 minutes post application. Subject considered a responder if the $\log_{10}$ CFU/cm^2 reduction of bacteria of groin areas was at least 3 and abdominal areas was at least 2. • No direct association of reduction of bacteria in pivotal studies with reduction in SSIs.	NDA submission demonstrates that anti-microbial reduction meets benchmarks for approval outlined in applicable TFMs, FR, and other FDA guidance. Skin preparation with alcohol based antiseptics as a preventive measure for hospital associated infections is recognized by the CDC as a Category IA recommendation, making it a strong recommendation supported by high quality evidence.
Risk and Risk Management	• Pivotal studies had low numbers of adverse events after application of ZuraPrep™. ZX-ZP-0073 with zero reported, and ZX-ZP-0074 with 7 reported, none serious. • 4 serious AEs were reported for ZuraPrep™ clinical program, none for pivotal studies and none related to test products. • Inclusion and exclusion criteria ensured a generally healthy and diverse study population in regards to the skin. • Phototoxicity and Photosensitivity (ZX-ZP-0016, ZX-ZP-0019) testing was done since ZuraPrep™ absorbed light at wavelengths of 290 to 700 nm. Neither study showed potential for phototoxicity or photosensitivity • Case reports showed MB being associated with skin necrosis when	The submitted safety studies focused on the risk of adverse skin reactions that might be expected with topical application of ZuraPrep™. The studies were appropriately conducted and did not identify any unexpected skin reactions or safety signals. AEs reported from the safety population were low in number and acuity. The safety profile overall matched or exceeded the safety profile of the RLD (ChloraPrep®) used in the studies. No safety issues or signals were identified that would preclude approval of this NDA for ZuraPrep™.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	directly injected into tissue to identify lymph nodes for certain surgical procedures. • Non-clinical testing did not detect MB in plasma after 21 days of dermal application on mini-pigs.	

1.4. Patient Experience Data

As defined in the 21st Century Cures Act, the term "patient experience data" includes data that:

> "(1) are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and (2) are intended to provide information about patients' experiences with a disease or condition, including the impact of such disease or condition, or a related therapy, on patients' lives; and patient preferences with respect to treatment of such disease or condition."

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Despite advances in infection control practices in the surgical setting, SSIs remain a substantial cause of morbidity, prolonged hospitalization, and death. SSIs are infections that occur during or after a surgery in the part of the body where the surgery took place and can involve the skin, tissues under the skin, organs, or implanted materials/devices. The National Healthcare Safety Network (NHSN) reported over 16,000 SSIs following nearly 850,000 operative procedures for an overall rate of 1.9% between 2006-2008.[1] In 2014 estimates of SSI incidence rates ranged from 2%-5%.[2] SSIs rank as the most costly of the hospital-acquired infections with an annual cost in the United States estimated at $3.5 to $10 billion.[3] According to the CDC, SSIs are associated with a mortality rate of 3%, with 75% of SSI-associated deaths being directly attributable to the SSI.[4]

2.2. Analysis of Current Treatment Options

Prevention of SSIs requires a multifaceted approach requiring the use of preventive measures before, during and after surgical procedures. Recommended interventions for the prehospital setting include preoperative bathing, smoking cessation, glucose control, MRSA screening, and when indicated, bowel preparations. Hospital setting interventions include glucose control, hair removal, proper skin preparation, proper surgical attire, antibiotic prophylaxis, intraoperative normothermia, wound protection, antibiotic sutures, topical antibiotics, supplemental oxygen and wound care[5]. As it relates to this NDA, the CDC's Prevention Guideline for the Prevention of Surgical Site Infection, 2017 categorizes the use of intraoperative skin preparation with an alcohol-based antiseptic agent as Category IA, making it a strong recommendation supported by high quality evidence. Currently, there are no FDA approved preoperative skin preparation products that contain IPA as the sole active ingredient that have been approved through the NDA process. Most similar preoperative skin preparations contain a combination of IPA and another active

[1] Mu Y, Edwards JR, Horan TC, Berríos-Torres SI, Fridkin SK. Improving risk-adjusted measures of surgical site infection for the National Healthcare Safety Network. Infect Control Hosp Epidemiol. 2011;32(10):970-986.
[2] Anderson DJ, Podgorny K, Berrios-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014; 35:605e627.
[3] Anderson DJ, Podgorny K, Berrios-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014; 35:605e627.
[4] Awad, S.S., "Adherence to surgical care improvement project measures and post-operative surgical site infections". Surgical Infection (Larchmt), 13(4): (2012): 234-7.
[5] Kristen A. Ban, Joseph P. Minei, Christine Laronga, Brian G. Harbrecht, Eric H. Jensen, Donald E. Fry, Kamal M.F. Itani, E Patchen Dellinger, Clifford Y. Ko, Therese M. Duane, American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update, Journal of the American College of Surgeons, Volume 224, Issue 1, 2017, Pages 59-74.

ingredient with many containing either chlorhexidine or iodine in varying concentrations. For this NDA, the sponsor chose ChloraPrep® (IPA 70% v/v, Chlorhexidine gluconate 2% w/v) as a control product for its studies.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Preoperative skin preparation products are approved through the NDA process or marketed via the monograph system. Although not proposed as a monograph product, this 505(b)(2) NDA submission follows requirements outlined in the 1994 proposed TFM for OTC antiseptic drug products[6]. NDA 210872 includes studies consistent with the May 2015, TFM amendment proposing additional safety data to support the safety of antiseptic active ingredients derived from in vitro data characterizing the active ingredient antimicrobial properties and in vivo clinical studies meeting specified criteria of log reductions in bacterial counts[7]. ZuraPrep™ is not yet approved for use in the U.S. or internationally.

3.2. Summary of Presubmission/Submission Regulatory Activity

The IND associated with this NDA was IND 117045. Pre-IND 117045 type B meeting was held on April 16, 2013 with application for IND being submitted on April 16, 2014 with NDA subsequently being submitted on June 29, 2018.

The most relevant issues identified for further investigation by the FDA during Pre-IND/IND review process included the following:

- identification of the active ingredients in ZuraPrep™ for appropriate evaluation of bactericidal activity, and effective concentration range
- waiver of phototoxicity and photoallergenicity studies
- demonstration of the safety of the topical use of MB.

(b) (4)

[redacted]

[6] FDA (1994). Tentative Final Monograph for OTC Health-Care Antiseptic Drug Products; Proposed Rule. 21 CFR Parts 333 and 369. https://www.gpo.gov/fdsys/pkg/FR-1994-06-17/html/94-14503.htm
[7] Federal Register, Vol. 80, No. 84, Friday, May 01, 2015, Department of Health and Human Services, FDA. 21 CFR Part 310. Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the- Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record. https://www.gpo.gov/fdsys/pkg/FR-2015-05-01/pdf/2015-10174.pdf

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(b) (4)

Filing review for NDA 210872 was completed on August 27, 2018. Filing review issues and information requests for statistics, regulatory, and clinical pharmacology are as follows:

Statistics – FDA statistics requested clarification of analyses for studies ZX-ZP-0073 and ZX-ZP-0074 as submitted analyses did not follow the submitted planned analyses for efficacy. In addition the FDA asked for clarification of discrepancies in site numbers. Sites being where the products were applied on the subjects (i.e. abdomen, groin).

Regulatory – Under 21 CFR 314.54(a)(1)(vi), a 505(b)(2) application must contain a patent certification or statement with respect to any relevant patents that claim the listed drug or that claim any other drugs on which the investigations relied on for approval of the application were conducted, or that claim a use for the listed or other drug. The sponsor's 505(b)(2) application relied upon the Agency's finding of safety and effectiveness for NDA 020832 ChloraPrep® (CHG 2%, IPA 70%), but did not contain patent certifications or statements with respect to each patent listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) for ChloraPrep® . The FDA requested the sponsor submit patent certifications or statements for those patents.

Clinical Pharmacology – The FDA had concerns about the adequacy of the literature data to support the evaluation of the in vivo absorption of IPA from ZuraPrep™ and its ability to bridge information to the RLD product. The FDA requested the sponsor submit any additional supportive material (e.g., results of an in vitro permeation study or an in vivo human pharmacokinetic study) and explanations as to how the information submitted will support the establishment of such a bridge.

The FDA also confirmed in this review that this NDA was exempt from PREA (21 U.S.C. 355c).

The FDA label review done by DMEPA on September 25, 2018 concluded that the proposed proprietary name was not acceptable (b) (4) (b) (4). The decision to deny the name was communicated to the sponsor on September 26, 2018. The sponsor responded by changing the proprietary name to ZuraGard and

submitting a request for review on December 6, 2018. ZuraGard is recognized as the newly approved proprietary name, but as previously submitted supportive documents uses the proprietary name ZuraPrep™, this review will continue to use ZuraPrep™ to avoid confusion.

The FDA sent an information request on November 1, 2018 in regards to CMC review issues. CMC noted that the drug (b) (4) had not submitted a leachable residue study for these materials. The FDA requested leachable information for these materials using the drug product (b) (4). In addition, CMC also requested more information for seal integrity and device pyrogenicity.

Zurex has responded to all requests for information and adequately addressed the issues identified during this review process.

3.3. Foreign Regulatory Actions and Marketing History

ZuraPrep™ is not approved for use internationally and sponsor reports no international marketing of proposed product.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI audit was not requested.

4.2. Product Quality

With the exception of a proprietary name change, the drug product used in the clinical development program will be the same as the one to be marketed. No quality issues were identified in this review that would impact approval of this drug. A full review of CMC deferred to the CMC Reviewer.

4.3. Clinical Microbiology

As discussed in section 3.2, the final to be marketed version of ZuraPrep™ needed to demonstrate bactericidal activity and demonstrate the effective concentration range or dose response of the product for a variety of clinically relevant organisms as described in TFM recommendations and guidelines. Bactericidal activity demonstrated in Pilot and Pivotal studies of efficacy and safety support approval of this drug.

4.4. Nonclinical Pharmacology/Toxicology

The only original nonclinical data required by FDA were those from a 21-day dermal toxicity study in minipigs (ZX-ZP-0003) that measured dermal response and absorption of MB. The FDA had approved PROVAYBLUE® (MB injection, 5 mg/mL) (NDA 204630) on April 8, 2016 with an indication for the treatment of pediatric and adult patients with acquired methemoglobinemia. Approved labeling for PROVAYBLUE® described nonclinical safety findings including positive signals in in vitro and in vivo genetic toxicity studies, oral embryofetal development studies in rats and rabbits, and 2-year oral carcinogenicity studies in rats and mice. The label for PROVAYBLUE® identifies MB as a carcinogen and induces abortions and malformations. DNDP Pharmacology/Toxicology concluded in their review that the proposed levels of MB do not raise safety concerns from the nonclinical perspective, as MB was not detected in plasma following repeated dermal application in the minipig toxicity study (ZX-ZP-0003).

4.5. Clinical Pharmacology

Clinical Pharmacology had concerns about the evaluation of in vivo absorption of IPA, more specifically, the adequacy of the literature data cited by the sponsor to support the evaluation of the in vivo absorption of IPA from ZuraPrep™ and its ability to bridge information to the RLD product. The products used in the literature provided were not identical to those found in ZuraPrep™, and the studies in the literature do not appear to be sufficient to allow for a cross-studies comparison (i.e., dermal absorption of IPA with versus without the presence of chlorhexidine gluconate). A request for additional supporting materials was made to the sponsor. To address this issue the sponsor conducted a study, The In Vitro Percutaneous Absorption of [14C]-IPA in Two Formulations Through Human Skin, Including a Volatility Assessment (ZX-ZP-0099). Response to this request for information was submitted on December 12, 2018 using the results of this study to demonstrate the level of absorption of IPA.

4.6. Devices and Companion Diagnostic Issues

As discussed in section 3.2, FDA CMC requested more information regarding leachables (b) (4)

4.7. Consumer Study Reviews

As discussed in section 3.2, DMEPA concluded that the proposed proprietary name was not acceptable (b) (4) (b) (4). The rationale for this change is available in section 8.7.3. The sponsor responded by changing the proprietary name to ZuraGard. ZuraGard is recognized as the newly approved proprietary name.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 1
Table of Clinical Studies

Study ZX-ZP#	Type	Description	N	Design/Control
0017	Cumulative Irritation	Evaluate the cumulative irritation potential of ZuraPrep™ and Vehicle over 21 days	40	Randomized, Within-Subject Comparison
0018	Contact Sensitization	Determine the allergic contact sensitization potential of ZuraPrep™ and Vehicle after repetitive patch applications to human subjects	225	Randomized, Within-Subject Comparison
0035	Pilot/Efficacy	Evaluation of effectiveness of topically applied ZuraPrep™ compared to positive control	64	Randomized, Open Label
0055	Pilot/Efficacy	Evaluation of safety and effectiveness of topically applied ZuraPrep™ compared to control	36	Randomized, Paired Comparison
ZX-ZP-0068	Pilot/Efficacy	Characterization of in vivo effects of ZuraPrep™ , Vehicle, reference product (ChloraPrep®), and Normal Saline	89	Randomized, Paired Comparison
0073	Pivotal Efficacy	Evaluation of the antimicrobial effectiveness of a single application of ZuraPrep™	440	Randomized, Paired Comparison
0074	Pivotal Efficacy	Evaluation of the antimicrobial effectiveness of a single application of ZuraPrep™	640	Randomized, Paired Comparison
0013	Antimicrobial Characterization	Evaluation of the dose response of the antimicrobial properties of ZuraPrep™, 5 ingredients and 2 controls	N/A	In Vitro Testing (Time Kill)
0014	Antimicrobial Characterization	Determination of the minimum inhibitory concentration and minimum bactericidal concentration of ZuraPrep™ and vehicle compared to controls	N/A	In Vitro Testing
0015	Antimicrobial Characterization	Evaluation for the antimicrobial properties of 2 test products, ZuraPrep™ and vehicle, compared to controls	N/A	In Vitro Testing (Time Kill)
0043	Bacterial Resistance characterization	Evaluation of potential for development of antimicrobial resistance	N/A	In Vitro Testing
0016	Photo-irritation potential	Determination of the irritation potential of topical application of ZuraPrep™ and Vehicle followed by light exposure	34	Single-center, controlled, randomized, within-subject comparison study
0019	Photo-allergic induction	Determination of the ability of ZuraPrep™ and vehicle to induce a photoallergic skin reaction using a controlled photopatch testing procedure	55	Single-center, controlled, randomized, within-subject comparison study
0083	Application Evaluation	Evaluation of proposed coverage area and dry time of a single ZuraPrep™ 10.5-mL applicator	20	Open-label single treatment

5.2. Review Strategy

Approvability for ZuraPrep™ relied on examination of the findings in the pivotal studies and other safety related studies conducted by the sponsor. The sponsor also submitted over 100 other literature references covering a wide range of topics in support of this NDA. These additional references were in general supportive of the safety and efficacy of IPA antiseptic products, but did not impact the determination of the approvability of this NDA.

Efficacy was assessed based on clinical studies demonstrating that a sufficient amount of bacteria were killed between the period of time between topical application of ZuraPrep™ plus drying of on intact skin and the start of a surgical procedure. Safety was assessed mainly on dermally related AEs that might be associated with the topical application of ZuraPrep™.

The active ingredient for ZuraPrep™ is IPA 70% v/v. IPA's efficacy and safety as an active ingredient in antiseptic products has been demonstrated in previously approved NDAs for similar antiseptic products with IPA as an active ingredient. Evaluation of efficacy and safety for ZuraPrep™ relied mainly on the pivotal studies (ZX-ZP-0073, ZX-ZP-0074) that compared ZuraPrep™ to the previously approved RLD, ChloraPrep® (NDA 020832) that contains the same concentration of IPA (70% v/v) as ZuraPrep™. This evaluation of efficacy required review by Pharm/Micro of clinical and invitro studies of the bactericidal activity of ZuraPrep™ to ensure that the bacterial reductions and kill times met TFM criteria as well as FDA specific guidance.

In regards to safety, this evaluation focused on dermal AEs that might be expected for a topically applied drug. To that end, focus was placed on studies evaluating dermal absorption of drug (IPA, MB) and potential skin irritation that might arise. The sponsor completed a 21-day dermal minipig study (ZX-ZP-0003) which confirmed plasma concentrations of MB were well below the lower limits of quantitation using a validated assay after the initial dose, as well as, after 21 consecutive days of dosing. PharmTox review found that study ZX-ZP-0003 confirmed plasma concentrations of MB were well below the lower limits of quantitation and did not raise safety concerns. IPA absorption was evaluated in study ZX-ZP-0099 (The In Vitro Percutaneous Absorption of [14C]-IPA in Two Formulations Through Human Skin, Including a Volatility Assessment) at the request of ClinPharm. The sponsor concluded that the absorption profiles for ZuraPrep™ and ChloraPrep® were comparable with each other. Pivotal studies (ZX-ZP-0073, ZX-ZP-0074) were used to evaluate AEs that occurred after application of ZuraPrep™ with a focus on local dermal events over the application sites. As ultraviolet-visible light scan of the final formulation of ZuraPrep™ showed light absorption corresponding to wavelengths of (b) (4) to (b) (4) nm, the sponsor also conducted studies for phototoxicity and photo-allergenicity (ZX-ZP-0016, ZX-ZP-0019).

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Pivotal Clinical Evaluation of the Antimicrobial Effectiveness of Topically Applied ZuraPrep™ (ZX-ZP-0073)

6.1.1. Study Design

Overview and Objective

The primary objective of this study was to measure the antimicrobial effectiveness of a single investigational product, ZuraPrep™10.5 mL Applicator as specified by FDA TFM for Health-Care Antiseptic Drug Products (vol. 59, No. 116, June 17, 1994, pp. 31450-31452), ASTM E1173 – 15 Standard Test Method for Evaluation of Preoperative, Precatheterization, or Preinjection Skin Preparations, and updated procedures specified by the FDA CDER. At 10 minutes, post-prep the investigational product should achieve a 70% responder rate to be considered a therapeutically effective antimicrobial agent. Additionally, the subjects were evaluated at 30 seconds and 6 hours post-prep as a secondary endpoint. A positive and negative control were evaluated using the same methodology.

Trial Design

This study utilized a randomized, paired comparisons design where each subject received at least 2 of the planned treatments. The 5" × 5" test site within the abdominal region (abdominal test area) was defined as the area below the umbilicus and above the groin. The 1.5" × 5" test site within the groin region (groin test area) was defined as the inner aspect of the upper thigh within and parallel to the inguinal crease below the groin. This study was performed according to the guidelines from the FDA TFM for Effectiveness Testing of a Patient Preoperative Skin Preparation (FR 59:116, 17 June 94, pp. 31450-31452), and ASTM E 1173-15, Standard Test Method for Evaluation of Preoperative, Precatheterization, or Preinjection Skin Preparations. Study site was located in the United States in Sterling, VA. No issues were identified related to study site that would preclude applicability of results of this study to the U.S. population.

All inclusion criteria were appropriate and consistent with guidelines outlined in the FDA TFM for Effectiveness Testing of a Patient Preoperative Skin Preparation (FR 59:116, 17 June 94, pp. 31450-31452). Key inclusion criteria for subjects to enroll in this study included the following:

- Male or female, at least 18 years or older.
- Were in good general health.
- Had skin within 6 inches of the test sites that were free of tattoos, dermatoses, abrasions, cuts, lesions or other skin disorders.

- Had Screening Day baseline counts of at least 1.0 x 10^3 CFU/cm^2 per abdominal site (left and right) and at least 1.0 x 10^5 CFU/ cm^2 per groin site (left and right).

All exclusion criteria were appropriate and consistent with guidelines outlined in the FDA TFM for Effectiveness Testing of a Patient Preoperative Skin Preparation (FR 59:116, 17 June 94, pp. 31450-31452). Key exclusion criteria for subjects to be excluded from this study included the following:

- Topical or systemic antimicrobial exposure from within 14 days prior to Screening Day through the remainder of the study. Restrictions included, but were not limited to antimicrobial soaps, antiperspirants/deodorants, shampoos, lotions, perfumes, after shaves, colognes, and topical or systemic antibiotics.
- Had contact with solvents, acids, bases, fabric softener-treated clothing or other household chemicals in the applicable test areas from within 14 days prior to Screening Day through the remainder of the study.
- Subjects who had a history of sensitivity to natural rubber latex, adhesive skin products (e.g., Band-Aids, medical tapes), IPA, citric acid, MB, methylparaben, propylparaben, or chlorhexidine gluconate products.
- Subjects who had a history of skin allergies.
- Subjects who had showered or bathed within 72 hours of the Screening Day or Treatment Day (sponge baths may have been taken, however, the lower abdomen and upper thigh region must have been avoided).
- Subjects who received an irritation score of 1 for any individual skin condition prior to the Screening Day baseline or Treatment Day baseline sample collection.
- Participated in another clinical trial in the 30 days prior to the Treatment Day of this study (treatment with test materials in this study), or were currently enrolled in another clinical trial, or had previously participated in this study.

Treatments procedures for this study were as follows:

ZuraPrep™ 10.5 mL Applicator– One pre-weighed applicator per site was applied topically by scrubbing for 2 minutes over a 1.5" x 5" area on the groin or scrubbing for 30 seconds over 5" x 5" area on the abdomen. Application was performed using repeated back and forth strokes of the sponge. Each test site was air-dried for 3 minutes. Post treatment weight of the applicator was recorded.

ChloraPrep® 10.5 mL Applicator - One pre-weighed applicator per site was applied topically by scrubbing for 2 minutes over a 1.5" x 5" area on the groin or scrubbing for 30 seconds over 5" x 5" area on the abdomen. Application was performed using repeated back and forth strokes of the sponge. Each test site was air-dried for 3 minutes. Post treatment weight of the applicator was recorded.

ZuraPrep™ Vehicle – 10.5mL of ZuraPrep™ Vehicle was added aseptically to the pre-weighed empty applicator for use per site and applied topically by scrubbing for 2 minutes over a 1.5" x 5" area on the groin or scrubbing for 30 seconds over 5" x 5" area on the abdomen. Application was performed using repeated back and forth strokes of the sponge. Each test site was air-dried for 3 minutes. Post treatment weight of the applicator was recorded.

Doses were selected based on available data from previous studies and planned final applicator size. The area sizes selected to apply the drug are comparable to what would be expected for a wide range of surgical procedures. The application technique for the products adequately simulates application of antiseptic products prior to surgical procedures.

Treatment timing was based on the time points for the study and the dry time of the investigational products. The sample time 30 seconds, 10 minutes and 6 hours posttreatment were selected in order to address efficacy requirements for a preoperative skin preparation as described in the TFM (10 minutes and 6 hours) and requested by FDA (30 seconds). The sponsor reported that product placement on subjects was determined by a computer-generated randomization schedule.

Blinding procedures for this study applied to the investigators and staff. The investigational products were not blinded from the study staff performing the investigational product application or bacterial sample collections. As the products used had different tints, blinding would have been difficult if attempted. Staff who performed bacterial enumeration were blinded from the identification of treatment assignment. The study personnel performing the bacterial enumeration were not involved in the investigational product application or the collection of samples. The Raw Data Sheet sections of the CRF were maintained separately (from the pages within the CRF which include study treatment identifications) during the treatment phase of the study. The study staff performing the bacterial enumeration recorded counts directly onto the Raw Data Sheet pages of the CRF without accessing the subject study documentation folder containing the other CRF pages. Blinding procedures were adequate for this type of study.

Table 2 and Table 3 are included on the next page to highlight the important features of the trial design described above.

Table 2
Study Schedule, ZX-ZP-0073

Procedure	Approximate Day of Study						
	0	11	12	14	18	19	21
Consent form signed	x						
Skin assessment	x						
Non-antimicrobial personal hygiene kit provided	x						
Subjects commenced washout period	x						
Subjects stopped bathing or showering		x					
Test site hair removal (if required)			x				
Screening inclusion/exclusion criteria				x			
Skin irritation assessment (pre-screening)				x			
Screening sample taken				x			
Subjects stopped bathing or showering					x		
Test site hair removal (if required)						x	
Treatment Inclusion/exclusion criteria							x
Skin irritation assessment (pre-baseline)							x
Baseline sample collection							x
Application of Investigational Products							x
Skin irritation assessment (30 seconds post-							x
30 seconds sample collection							x
Skin irritation assessment (10 min post-treatment)							x
10 minute sample collection							x
Protective dressing application on treatment sites							x
Skin irritation assessment (6 hour post-treatment)							x
6 hour sample collection							x

Adapted from Table 1, ZX-ZP-0073, page 11

Table 3
Treatments, Anatomical Sites of Evaluation, Application and Dry Times and Coverage Areas

Treatment	Site	Application Time	Dry Time (minutes)	Area (inches)
ZuraPrep™10.5 mL Applicator	Abdomen	30 seconds	3	5x5
	Groin	2 minutes	3	1.5x5
ChloraPrep® 10.5 mL Applicator	Abdomen	30 seconds	3	5x5
	Groin	2 minutes	3	1.5x5
ZuraPrep™ Vehicle 10.5 mL applicator	Abdomen	30 seconds	3	5x5
	Groin	2 minutes	3	1.5x5

Adapted from Table 2, ZX-ZP-0073, page 11

Study Endpoints

At 10 minutes, post-prep the investigational product should achieve a 70% responder rate to be considered a therapeutically effective antimicrobial agent. Additionally, the subjects were evaluated at 30 seconds and 6 hours post-prep as a secondary endpoint. A positive and negative control were evaluated using the same methodology.

There were four primary efficacy objectives at the 10 minute time point:

1. Show that the lower bound of a 95% confidence interval for the responder rate of ZuraPrep™ for the abdomen is ≥ 70%.

2. Show that the lower bound of a 95% confidence interval for the responder rate of ZuraPrep™ for the groin is ≥ 70%.

3. To show effectiveness, ZuraPrep™ should be non-inferior to ChloraPrep® with a 0.5 margin. Specifically, the upper bound of the 95% confidence interval of the ATE of ChloraPrep® minus the ATE of ZuraPrep™ should be less than or equal to 0.5.

4. To show effectiveness, ZuraPrep™ should be superior to ZuraPrep™ vehicle by a 1.2 margin. Specifically, the lower bound of the 95% confidence interval of the ATE of ZuraPrep™ minus the ATE of ZuraPrep™ vehicle should be greater than or equal to 1.2.

Statistical Analysis Plan

log_{10} CFU/cm^2 reductions from baseline were calculated separately for each subject, postapplication time point, and body site, by subtracting the log_{10} CFU/cm^2 values for each postapplication time point from the log_{10} CFU/cm^2 values for the treatment day baseline. Responder status was calculated on a per body area basis. A left or right groin body area was considered a responder at 10 minutes if the log_{10} CFU/cm^2 reduction was at least 3.0. A left or right abdominal body area was considered a responder at 10 minutes if the log_{10} CFU/cm^2 reduction was at least 2.0. Responder status at 30 seconds was calculated the same way as the 10 minute responder status. A left or right body area (groin or abdomen) was considered a responder at 6 hours if the CFU values were below baseline (i.e. a log_{10} CFU/cm^2 reduction > 0). log_{10} CFU/ cm^2reductions from baseline and responder rates were grouped by body site, treatment, and post application sample time point.

Comparisons between products were performed by calculating differences in log_{10} CFU/cm^2 reductions from baseline and responder rates between treatments using the same statistical models. Average Treatment Effects (ATEs), non-inferiority, and superiority calculations were calculated by using a general linear regression (PROC GLM) on the log_{10} CFU values, adjusting for the treatment day baseline log_{10} CFU values to calculate log reductions from baseline.

Protocol Amendments

Two amendments were added to the protocol, neither considered significant or impactful.

6.1.2. Study Results

Compliance with GCP

Applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with GCP.

Financial Disclosure

Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

Patient Disposition

A total of 440 subjects were treated on the abdomen and groin. A total of 681 subjects were consented. Of these, 48 withdrew or were excluded prior to the screening day.

Screening microbiological samples were collected from 633 subjects. Only subjects with qualifying screening counts of at least 1.0 x 10^3 CFU/cm^2 per abdomen site (left and right) and 1.0 x 105 CFU/cm^2 per groin site (left and right) were treated. 452 of the 633 subjects had "qualifying screening counts" and 440 were treated. 11 qualified subjectswithdrew or were excluded prior to treatment day. There were 2 extra screened subjects. There were 344 subjects that had qualifying Treatment Day baseline counts on the groin (right and left) and the abdomen (right and left) and completed the study. 34 subjects had qualifying Treatment Day baseline counts only on the abdomen (right and left and five of them only on one side) and completed the study. 19 subjects had qualifying Treatment Day baseline counts only on the groin (right and left and two of them only on one side) and completed the study. This resulted in 751 evaluable abdomen sites and 724 evaluable groin sites.

Protocol Violations/Deviations

The sponsor reported 11 protocol deviations. Review of deviation descriptions showed that deviations were minor in nature and did not appear to have a major impact on study results or the safety of the study subjects.

Table of Demographic Characteristics, ZX-ZP-0073
Table 4

Demographic		**n=440**
Age (Years)	Mean	38.43
	Standard Deviation	15.32
	Minimum	18
	Maximum	80
Sex Frequency (Percent)	Male	250 (56.82%)
	Female	190 (43.18%)
Race Frequency (Percent)	White/Caucasian	176 (40.00%)
	Black/African-American	84 (19.09%)
	Hispanic	45 (10.23%)
	Asian	119 (27.05%)
	Other	16 (03.64%)

Adapted from Table 4, ZX-ZP-0073, page 22

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
Subjects were healthy adults with no other notable baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment was administered by staff personnel to reduce variability of treatment and to ensure compliance to treatment procedures. Subjects were required to return for sampling 6 hours after treatment. One protocol deviation noted that subject (b) (6) did not return for sampling of treatment site 6 hours after treatment. The reason for the subject not returning is unknown. No other reports of non-compliance on the part of subjects was noted.

Efficacy Results – Primary Endpoint

The primary measure of antimicrobial efficacy was the reduction of skin flora from baseline. The primary efficacy criteria was the responder rate at 10 minutes post-treatment for the abdomen and groin sites. The goal for responder rates was to have the lower bound of the 95% confidence interval be ≥ 70%. Product effectiveness was measured using the average treatment effects (ATE). The ATE was estimated from a linear regression of posttreatment bacterial count (log_{10} scale) at 10 minutes on the additive effect of a treatment indicator compared to the baseline or pretreatment measurement (log_{10} scale). To show effectiveness, the test product showed non-inferiority to ChloraPrep® with a 0.5 margin (log_{10} scale, upper bound of 95% confidence interval of the difference in ATE values ≤0.5) at 10 minutes and superiority to the vehicle control by a margin of 1.2 (log_{10} scale, lower bound of 95% confidence interval of the difference in ATE values ≥1.2) at 10 minutes. The primary efficacy goal was to have the confidence intervals for the 10 minute responder rates be ≥ 70%. Both active treatments met the target responder rate at 10 minutes for both the groin and abdomen as seen in Table 5.

Table 5
Non-Inferiority and Superiority Analysis ZX-ZP-0073

Body Area	Treatments	30 Seconds		10 Minutes	
		ATE Difference	95% CI	ATE Difference	95% CI
Groin	Non-inferiority (ChloraPrep® vs ZuraPrep™)	-0.078	(-0.264 to 0.108)	-0.039	(-0.184 to 0.106)
	Superiority – ZuraPrep™ vs Vehicle	2.300	(1.983 to 2.618)	2.595	(2.347 to 2.843)
	Superiority – ChloraPrep® vs Vehicle	2.222	(1.904 to 2.540)	2.556	(2.308 to 2.804)
Abdomen	Non-inferiority - ChloraPrep® vs ZuraPrep™	-0.111	(-0.238 to 0.016)	-0.021	(-0.096 to 0.054)
	Superiority – ZuraPrep™ vs Vehicle	1.892	(1.673 to 2.111)	1.870	(1.740 to 1.999)
	Superiority – ChloraPrep® vs Vehicle	1.781	(1.562 to 2.000)	1.849	(1.719 to 1.979)

Taken from Zurex reanalysis, 10/24/2018

Data Quality and Integrity

OSI audit was not requested. No data quality or integrity issues were identified.

Efficacy Results – Secondary and other relevant endpoints

The secondary measures of antimicrobial efficacy were the $\log_{10}$ CFU/cm^2 reductions from baseline, the responder rates, ATE values and differences in ATE values at 30 seconds. The noninferiority and superiority goals for ATE values are identical to those at 10 minutes. At 6 hours, a site was considered a responder if it was below baseline; otherwise, 6-hour responder rates were calculated identically to the 10-minute responder rates. The $\log_{10}$ CFU/cm^2 reductions from baseline goals were to have the 95% confidence intervals be ≥ 2.0 for the abdomen and 3.0 for the groin at 30 seconds and 10 minutes and be above 0 at 6 hours. The responder rate goal at 30 seconds and 6 hours was to have the lower bound of the 95% confidence interval be ≥ 70%. Both active treatments had a responder rate over 70% at 30 seconds for the abdomen. ZuraPrep™ had a responder rate over 70% at 30 seconds for the groin; ChloraPrep® did not achieve a 70% responder rate for the groin at 30 seconds. At 6 hours, ChloraPrep® had a 100% responder rate for both the abdomen and the groin. ZuraPrep™ had a 100% responder rate at 6 hours for the groin and 99% for the abdomen. The confidence intervals for each were above 70%. ZuraPrep™ met the non-inferiority and superiority criteria at 30 seconds. (See Table 1 under Efficacy Results – Primary Endpoints).

Additional Analyses Conducted on the Individual Trial

No additional analyses conducted for this study.

6.2. Pivotal Clinical Evaluation of ZuraPrep™, a Patient Preoperative Skin Preparation (ZX-ZP-0074)

6.2.1. Study Design

Overview and Objective

The purpose of this study was to evaluate the antimicrobial properties and safety of ZuraPrep™ with a positive control (ChloraPrep® 10.5 mL Applicator) and a negative control (ZuraPrep™ Vehicle) when used as a patient preoperative skin preparation. Testing was performed based upon procedures outlined in the FDA TFM for Effectiveness Testing of a Patient Preoperative Skin Preparation (Vol. 59, No. 116, June 17, 1994, pp. 31450-31452) and ASTM E1173-15 Evaluation of Preoperative, Precatheterization, or Preinjection Skin Preparations. The primary objective of this study was to evaluate antimicrobial efficacy based upon calculations of mean $\log_{10}$ reductions from baseline populations by subtracting the $\log_{10}$ number of viable microorganisms recovered at each post-product application sample from the $\log_{10}$ number of viable microorganisms recovered in the

baseline samples. The TFM indicated $\log_{10}$ CFU/cm^2 reductions as the primary efficacy measure while the Proposed Amendment of the TFM (FR 80:84, 01 May 2015) indicated responder rates as the primary efficacy requirement.

Trial Design

This study utilized a randomized, paired comparisons design where each subject received at least 2 of the planned treatments. The 5" × 5" test site within the abdominal region (abdominal test area) was defined as the area below the umbilicus and above the groin. The 1.5" × 5" test site within the groin region (groin test area) was defined as the inner aspect of the upper thigh within and parallel to the inguinal crease below the groin. ZuraPrep™ and the positive control, ChloraPrep® , were paired and evaluated with a sample size of at least 288 subjects. A minimum of 288 abdominal regions and 288 groin regions were treated with ZuraPrep™ on one side and ChloraPrep® on the other. The negative control (ZuraPrep™ Vehicle) was paired and evaluated with ZuraPrep™ and with the positive control, ChloraPrep® , with a sample size of at least 32 subjects for each pairing. A minimum of 64 abdominal regions and 64 groin regions were treated with the negative control (ZuraPrep™ Vehicle) on one side of the body and ZuraPrep™ or ChloraPrep® on the other for each pairing. Following a 14-day restriction period, subjects with sufficient resident bacterial flora were tested. A total of three post treatment sample collections were performed at each test site for all test materials. Specific sites of sampling and treatment groups were randomized. All subjects had samples collected at baseline. The test materials were applied bilaterally to the skin of the abdomen and/or the groin. Samples were collected at 30 seconds, 10 minutes, and 6 hours following completion of the product application procedure (including a 3-minute dry time) from anatomical treatment sites. Visual evaluations of skin reactions were conducted prior to baseline and prior to each sample interval. Plating for this study was conducted in duplicate using the pour plating technique by blinded laboratory personnel.

This study was performed according to the guidelines from the FDA TFM for Effectiveness Testing of a Patient Preoperative Skin Preparation (FR 59:116, 17 June 94, pp. 31450-31452), and ASTM E 1173-15, Standard Test Method for Evaluation of Preoperative, Precatheterization, or Preinjection Skin Preparations. Study site was located in the United States in Butte, MT. No issues were identified related to study site that would preclude applicability of results of this study to the U.S. population.

All inclusion criteria were appropriate and consistent with guidelines outlined in the FDA TFM for Effectiveness Testing of a Patient Preoperative Skin Preparation (FR 59:116, 17 June 94, pp. 31450-31452). Key Inclusion criteria for subjects to enroll in this study included the following:

- Male or female, at least 18 years or older.
- Were in good general health.

- Had skin within 6 inches of the test sites that was free of tattoos, dermatoses, abrasions, cuts, lesions or other skin disorders.
- Had Screening Day baseline counts of at least 1.0 x 10^3 CFU/cm^2 per abdominal site (left and right) and at least 1.0 x 10^5 CFU/ cm^2 per groin site (left and right).

All exclusion criteria were appropriate and consistent with guidelines outlined in the FDA TFM for Effectiveness Testing of a Patient Preoperative Skin Preparation (FR 59:116, 17 June 94, pp. 31450-31452). Key exclusion criteria for subjects to be excluded from this study included the following:

- Known allergies or sensitivities to sunscreens, deodorants, laundry detergents, topical application of fragrances, vinyl, latex (rubber), alcohols, metals, inks, or tape adhesives, or to common antibacterial agents found in soaps, lotions, or ointments, particularly chlorhexidine gluconate (CHG), citric acid, MB, methylparaben, propylparaben, or IPA.
- Exposure of test sites to strong detergents, solvents, or other irritants within the 14-day product-restriction period or during the test period.
- Exposure of test sites to antimicrobial agents, medicated soaps, medicated shampoos, or medicated lotions, use of biocide-treated pools or hot tubs, use of hot waxes or depilatories, including shaving (in the applicable test areas), use of tanning beds, or sunbathing during the 14-day product-restriction period or during the test period.
- Use of systemic or topical antibiotic medications, any inhaled or injection steroid medications, steroid medications (other than for hormonal contraception, for postmenopausal reasons, nasal spray, and eye drops), or any other product known to affect the normal microbial flora of the skin during the 14-day product-restriction period or during the test period.
- Subjects who had a history of skin allergies.
- Subjects who received an irritation score of 1 for any individual skin condition prior to the Screening Day baseline or Treatment Day baseline sample collection.

Treatments procedures for this study were as follows:

ZuraPrep™10.5 mL Applicator– One pre-weighed applicator per site was applied topically by scrubbing for 2 minutes over a 1.5" x 5" area on the groin or scrubbing for 30 seconds over 5" x 5" area on the abdomen. Application was performed using repeated back and forth strokes of the sponge. Each test site was air-dried for 3 minutes. Post treatment weight of the applicator was recorded.

ChloraPrep® 10.5 mL Applicator - One pre-weighed applicator per site was applied topically by scrubbing for 2 minutes over a 1.5" x 5" area on the groin or scrubbing for 30 seconds over 5" x 5" area on the abdomen. Application was performed using repeated back and forth strokes of the sponge. Each test site was air-dried for 3 minutes. Post treatment weight of the applicator was recorded.

ZuraPrep™ Vehicle – 10.5mL of ZuraPrep™ Vehicle was added aseptically to the pre-weighed empty applicator for use per site and applied topically by scrubbing for 2 minutes over a 1.5" x 5" area on the groin or scrubbing for 30 seconds over 5" x 5" area on the abdomen. Application was performed using repeated back and forth strokes of the sponge. Each test site was air-dried for 3 minutes. Post treatment weight of the applicator was recorded.

The amount of negative control and investigational product packaged and used was based on prior studies and products developed for skin preparation. The positive control was a marketed product. The area sizes selected to apply the drug are comparable to what would be expected for a wide range of surgical procedures. The application technique for the products adequately simulates application of antiseptic products prior to surgical procedures.

The study materials were not blinded from the Investigator or other study staff performing the study material application or bacterial sample collections. Technicians who participated in plating samples and/or counting colonies on plates resulting from testing did not participate in the test product application or sample collection procedures and were considered blinded. The blinding did not apply to baseline-screening samples. Blinding procedures were adequate for this type of study.

Treatment timing was based on the time points for the study and the dry time of the investigational products. The sample time 30 seconds, 10 minutes and 6 hours posttreatment were selected in order to address efficacy requirements for a preoperative skin preparation as described in the TFM (10 minutes and 6 hours) and requested by FDA (30 seconds).

Table 6 on the next page highlights the important features of the trial design described above.

Table 6
Study Schedule ZX-ZP-0074

Procedure	Day			
	-14 or more	-3 or more	0	3 or more (Treatment Day)
Informed Consent Obtained	X			
Product-Restriction Period	X	X	X	
Inclusion/Exclusion Criteria, Medical History Reviewed	X	X	X	
Visual Skin Assessment		X		
Clipping Hair from Test sites		X		
Visual Evaluation of Skin Reaction			X	
Baseline Screening			X	
Pregnancy Test Administered				X
Visual Evaluation of Skin Reaction				X
Test-Day Baseline Sample				X
Product Application				X
30-Second Post-Product Application Visual Evaluation of Skin Reaction				X
30-Second Post-Product Application Sample				X
10-Minute Post-Product Application Visual Evaluation of Skin Reaction				X
10-Minute Post-Product Application Sample				X
Sample Sites Bandaged				X
6-Hour Post-Product Application Visual Evaluation of Skin Reaction				X
6-Hour Post-Product Application Sample				X

Adapted from Table 1, ZX-ZP-0074, page 34

Study Endpoints

The primary endpoint was assessed based on the reduction of skin flora on the abdomen and groin sites 10 minutes following product application of the study treatments relative to the Treatment Day baseline counts. The reduction was first calculated as $\log_{10}$ CFU/cm^2 changes from baseline, then the percentage of successes were calculated from the $\log_{10}$ CFU/cm^2 reductions (i.e. percent of subjects meeting required reductions = responder rate). A site was considered a responder for the treatment at 10 minutes if it achieved a ≥ 2.0 $\log_{10}$ CFU/cm^2 reduction on the abdomen or ≥ 3.0 $\log_{10}$ CFU/cm^2 reduction on the groin.

Responder status was calculated separately for the abdomen and groin, for each investigational product, for each treatment sample time, and for each subject. The individual responses were then grouped to generate an overall responder rate for each anatomical area, for each investigational product, and for each post-treatment sample time. The efficacy goal for active products was to have the lower bound of the 95% confidence interval for the responder rate to be greater than or equal to 70%. As recommended by FDA, product effectiveness was measured using the ATE. The ATE was estimated from a linear regression of posttreatment bacterial count (log_{10} scale) at 10 minutes of the additive effect of a treatment indicator and the baseline or pretreatment measurement (log_{10} scale). To show effectiveness, the investigational product would have been 1) non-inferior to ChloraPrep® with a 0.5 margin (log_{10} scale scale, upper bound of 95% confidence interval of the difference in ATE values ≤ 0.5) and 2) superior to the vehicle control by a margin of 1.2 (log_{10} scale scale, lower bound of 95% confidence interval of the difference in ATE values ≥ 1.2).

Secondary endpoints examined ATE values at 30 seconds. The non-inferiority and superiority goals for ATE values at 30 seconds were identical to those at 10 minutes. At 6 hours a site was considered a responder if it was below baseline; otherwise, 6-hour responder rates were calculated identically to the 10-minute responder rate. The secondary efficacy goals were to have the 95% confidence interval for the responder rates be greater than or equal to 70%. log_{10} CFU/cm^2 reductions from baseline were also calculated for all post-prep samples.

Statistical Analysis Plan

The Intent-to-Treat (ITT) Population consisted of all subjects who passed the pre-test period prior to baseline screening and were assigned a subject number for treatment. The ITT population (all randomized subjects) were used for the safety analysis. The modified Intent-to-Treat (mITT) Population consisted of all subjects who had at least one site (left or right for abdominal or groin) that passed the treatment day baseline (baseline values between 3.0 log_{10} - 5.5 log_{10} CFU/cm^2 on the skin on the abdomen, or 5.0 log_{10} - 7.5 log_{10} CFU/ cm^2 on the skin on the groin) and had CFU results for any other sample time for that site. The mITT data set included all sites that passed the treatment day baseline bacterial counts and had CFU results for any other sample time. The mITT data set was evaluated for efficacy.

Individual plate CFU count changes from baseline were calculated separately for each subject and for each of the three non-baseline sites by taking the baseline log_{10} CFU/cm^2 values and then subtracting the log_{10} CFU/cm^2 values for the samples taken after the baseline. Responder status was calculated for each reported log_{10} CFU/cm^2 reduction. The sites were considered responders based on the sample time and body area:

- For the groin at 10 minutes, a $\log_{10}$ CFU/cm^2 reduction ≥ 3.0 was considered a responder.
- For the abdomen at 10 minutes, a $\log_{10}$ CFU/cm^2 reduction ≥ 2.0 was considered a responder.

Responder statuses were grouped by body area, sample time, and test substance. Exact confidence intervals were calculated for responder rates. The primary efficacy goal was to have the 95% confidence intervals for the responder rate at 10 minutes of ≥ 70%. Differences in responder rates between treatments and their confidence intervals were calculated using asymptotic (approximate) methods. If differences in responder rates were not reliable based on approximate methods, which could happen when rates were near either 100% or 0%, $\log_{10}$ CFU/cm^2 confidence intervals for the differences were used for comparison instead. Two-sided confidence intervals for $\log_{10}$ CFU/cm^2 changes from baseline were also calculated. These calculations used an ANOVA model with subject as a random variable and test substance as a fixed variable. Body area (abdomen or groin) was a fixed variable. Sample times (30 seconds, 10 minutes, or 6 hours) were calculated separately using identical models. Differences in $\log_{10}$ CFU/cm^2 reductions were calculated based on the same model. Additionally, as recommended by FDA, product effectiveness was measured using the ATE. The ATE was estimated from a linear regression of post-treatment bacterial count ($\log_{10}$ scale) at 10 minutes on the additive effect of a treatment indicator and the baseline or pretreatment measurement ($\log_{10}$ scale). To show effectiveness, the ZuraPrep™ needed to be non-inferior to ChloraPrep® with a 0.5 margin ($\log_{10}$ scale, upper bound of 95% confidence interval of the difference in ATE values ≤ 0.5) and superior to the vehicle control by a margin of 1.2 ($\log_{10}$ scale, lower bound of 95% confidence interval of the difference in ATE values ≥ 1.2).

Secondary time points for the study were 30-seconds and 6-hours post-application. The secondary efficacy goals were to have the 95% confidence intervals for the responder rates be greater than or equal to 70% for both the abdomen and groin. ATE value calculated at 30 seconds were similar to 10 minutes with the same criteria applied. Log_{10} reductions from baseline were also calculated for all post-prep samples.

Protocol Amendments

5 amendments were added to the protocol, none considered significant or impactful.

6.2.2. Study Results

Compliance with GCP

Applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with GCP.

Financial Disclosure

Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

Patient Disposition

A total of 2,227 subjects were recruited/consented for the study. Of these, a total of 1,612 were clipped and 1,526 were screened for baseline. Of the 1,526 subjects screened, 641 subjects were randomized, 640 subjects were treated, and 639 subjects completed testing. Of the 640 subjects treated, 67 subjects were baseline failures on all sites, therefore, the number of subjects used in the efficacy analysis was 573. Subjects were enrolled in pre-defined randomization blocks. Randomization was conducted separately for abdomen and groin sites resulting in 13 blocks of 571 subjects in the abdomen and 11 blocks of 485 subjects in the groin. All subjects that began test day procedures received treatments with the exception of one subject who experienced an AE following the first baseline sample (prior to product application). All subjects that were treated completed the study with the exception of one subject who did not return for the 6-hour samples.

Protocol Violations/Deviations

Table 7, Deviation Categories, ZX-ZP-0074

Deviation Category	Number of Deviations
Subject enrollment <30 days after previous clinical trial participation	4
Designated training applicator use in testing	2
Randomization deviations	11
Irritation dismissal error	6
30-second and 10-minute sampling time exceptions	5
6-hour sampling time exceptions	5
Incubation duration exceptions	3
Cylinder Sampling (Scrub Cup) Technique errors	7
Treatment day samples plated beyond 30 minutes	5
Product application error	1
Plating technician blinding compromised	3
Total	52

Review of deviation descriptions showed that deviations were minor in nature and did not have impact on study results or the safety of the study subjects.

Table of Demographic Characteristics

Table 8
Demographic Characteristics ZX-ZP-0074

Demographic Category	Screened	Received Product	Completed Testing
Age			
Minimum Age	18	18	18
Median Age	27	30	30
Maximum Age	85	85	85
Sex			
Males	863	476	475
Females	663	164	164
Total	1526	640	639
Race			
White/Caucasian	1382	576	575
Native American Indian/Alaskan Native	38	15	15
African American	14	9	9
Asian	28	8	8
Native Hawaiian/Pacific Islander	0	0	0
Other	24	9	9
Subject Chose Not to Disclose	40	23	23
Ethnicity			
Non-Hispanic/Non-Latino	1401	581	580
Hispanic/Latino	48	20	20
Subject Chose Not to Disclose	77	39	39

Adapted from Table 5, ZX-ZP-0074, page 58

Overall, the subjects screened and who received product, adequately represented the demographics of the general population that might be expected to use ZuraPrep.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
Subjects were healthy adults with no other notable baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Subjects were questioned prior to and during the study to ensure compliance with study requirements. The investigator and/or designated contract laboratory personnel applied all test materials according to the application instructions and randomization schedule. Laboratory personnel verified the dose applied by weighing the product applicator before and following application and recording the measurements. Details of the exact application, and time of study test material administration were documented in the applicable study records. The study also was routinely audited by the contracted laboratory Quality Assurance at regular intervals to assure compliance, as well as by the Sponsor's clinical research associates.

Efficacy Results – Primary Endpoint

Efficacy was evaluated based on 10 minutes post application as the primary efficacy time point, specifically, to have the lower bound of the 95% confidence interval for the responder rate to be greater than or equal to 70%. Non-inferiority to the active comparator and superiority to the vehicle at 10 minutes was an additional primary endpoint. ZuraPrep™ achieved the 70% responder rate requirement in the abdomen and groin. The lower bound of the 95% confidence interval for the 10 minute responder rate for ZuraPrep™ exceeded 70% for both the abdomen and the groin. The upper bound of the 95% confidence interval of the ATE of ChloraPrep® minus the ATE of ZuraPrep™ at 10 minutes was ≤ 0.5 for both the abdomen and groin. ZuraPrep™ was considered non-inferior to ChloraPrep® at this time-point. The lower bound of the 95% confidence interval of the ATE of ZuraPrep™ minus the ATE of the ZuraPrep™ Vehicle at 10 minutes was ≥ 1.2 for both the abdomen and groin. ZuraPrep™ was considered superior to its vehicle at this time-point. Table 9 on the next page summarizes these findings.

Table 9
Non-Inferiority and Superiority Analysis

Body Area	Treatments	30 Seconds		10 Minutes	
		ATE Difference	95% CI	ATE Difference	95% CI
Groin	Non-inferiority (ChloraPrep® vs ZuraPrep™)	-0.024	(-0.217 to 0.169)	-0.020	(-0.212 to 0.172)
	Superiority – ZuraPrep™ vs Vehicle	2.609	(2.283 to 2.934)	2.454	(2.129 to 2.778)
	Superiority – ChloraPrep® vs Vehicle	2.584	(2.259 to 2.909)	2.434	(2.110 to 2.757)
Abdomen	Non-inferiority - ChloraPrep® vs ZuraPrep™	-0.023	(-0.196 to 0.150)	-0.045	(-0.208 to 0.117)
	Superiority – ZuraPrep™ vs Vehicle	2.048	(1.756 to 2.341)	1.972	(1.697 to 2.247)
	Superiority – ChloraPrep® vs Vehicle	2.025	(1.733 to 2.318)	1.927	(1.651 to 2.202)

Taken from Zurex reanalysis, 10/24/2018

Data Quality and Integrity

OSI audit was not requested. No data quality or integrity issues identified.

Efficacy Results – Secondary and other relevant endpoints

The lower bound of the 95% confidence interval for the 30 second responder rate for ZuraPrep™ exceeded 70% for the abdomen, but for the groin the mean was above 70% but the confidence interval was not. The lower bound of the 95% confidence interval for the 30 second $\log_{10}$ CFU/cm^2 reduction from baseline for ZuraPrep™ exceeded 2.0 for the abdomen and exceeded 3.0 for the groin.

Table 10
Responder Rate – Groin Site, 30 Seconds, ZX-ZP-0074

Products	Failed	Total	Passed	Responder Rate	95% CI Lower	95% CI Upper
ZuraPrep™	100	343	243	70.8%	65.7%	75.6%
ChloraPrep®	102	352	250	71.0%	66.0%	75.7%
Vehicle	73	74	1	1.4%	0.0%	7.3%

Adapted from Table 14 , ZX-ZP-0074, page 63

Table 11
Responder Rate – Abdominal Site, 30 Seconds, ZX-ZP-0074

Product	Failed	Total	Passed	Responder Rate	95% CI Lower	95% CI Upper
ZuraPrep™	76	324	248	76.5%	71.5%	81.1%
ChloraPrep®	76	320	244	76.3%	71.2%	80.8%
Vehicle	65	68	3	4.4%	0.9%	12.4%

Adapted from Table 16, ZX-ZP-0074, page 63

The upper bound of the 95% confidence interval of the ATE of ChloraPrep® minus the ATE of ZuraPrep™ at 30 seconds was ≤ 0.5 for both the abdomen and groin. ZuraPrep™ was considered non-inferior to ChloraPrep® at this time-point. The lower bound of the 95% confidence interval of the ATE of ZuraPrep™ minus the ATE of the ZuraPrep™ Vehicle at 30 seconds was ≥ 1.2 for both the abdomen and groin. ZuraPrep™ was considered superior to its vehicle at this time-point (See Table 2 under Efficacy Results – Primary Endpoints).

The lower bound of the 95% confidence interval for the 6-hour responder rate for ZuraPrep™ exceeded 70% for both the abdomen and the groin. The 95% confidence interval for the 6- hour $\log_{10}$ reduction from baseline for ZuraPrep™ were entirely above 0 at 6 hours for both the abdomen and the groin.

Table 12
Responder Rate – Groin Site, 30 Seconds, ZX-ZP-0074

Products	Failed	Total	Passed	Responder Rate	95% CI Lower	95% CI Upper
ZuraPrep™	0	343	343	100%	99.1%	100%
ChloraPrep®	2	352	350	99.4%	98.0%	99.9%
Vehicle	0	74	74	100%	96.0%	100%

Adapted from Table 18, ZX-ZP-0074, page 64

Table 13
Responder Rate – Abdominal site, 6 hours, ZX-ZP-0074

Products	Failed	Total	Passed	Responder Rate	95% CI Lower	95% CI Upper
ZuraPrep™	3	324	321	99.1%	97.3%	99.8%
ChloraPrep®	3	320	317	99.1%	97.3%	99.8%
Vehicle	9	68	59	86.8%	76.4%	93.8%

Adapted from Table 20, ZX-ZP-0074, page 65

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Table 14
Efficacy Endpoints, ZX-ZP-0073/0074

Study	Efficacy Endpoints	
	Primary	**Secondary/Other**
Pivotal Studies		
ZX-ZP-0074	• Percentage of responders[a] at 10 minutes post application • ATE[b] at 10 minutes post application	• Percentage of responders[a] at 30 seconds and 6 hours post application • Log_{10} CFU/cm^2 reduction at each post application sampling time • ATE[b] at 30 seconds post application
ZX-ZP-0073	• Percentage of responders[a] at 10 minutes post application • ATE[b] at 10 minutes post application	• Percentage of responders[a] at 30 seconds and 6 hours post application • Log_{10} CFU/cm^2 reduction at each post application sampling time • ATE[b] at 30 seconds post application

[a] Responder at 30 seconds and 10 minutes was defined as reduction ≥2 log_{10} CFU/cm^2 on the abdomen or ≥3 log_{10} CFU/cm^2 on the groin. Responder at 6 hours for abdomen and groin was defined as below baseline value.

[b] The ATE was estimated from a linear regression of posttreatment bacterial count (log_{10} scale) at 30 seconds and 10 minutes on the additive effect of a treatment indicator and the baseline or pretreatment measurement (log_{10} scale).

Adapted from Table 3, ISE, page 15

Primary endpoints were adapted from the 2017 Final Rule for Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use.[8]

7.1.2. Secondary and Other Endpoints

The secondary measures of antimicrobial efficacy were the log_{10} CFU/cm^2 reductions from baseline, the responder rates, ATE values and differences in ATE values at 30 seconds and 6 hours post application of ZuraPrep™. Surgical incisions are intended to be made after the topical application of ZuraPrep™ completely dries, but urgent or emergency situations may

[8] Federal Register, Vol. 82, No. 243, Wednesday, December 20, 2017, Department of Health and Human Services, FDA. 21 CFR Part 310. Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the- Counter Human Use; Final Rule; https://www.govinfo.gov/content/pkg/FR-2017-12-20/pdf/2017-27317.pdf

arise where an incision needs to be made sooner. The secondary endpoint at 30 seconds demonstrates efficacy of ZuraPrep™ when incisions are made before the skin has completely dried. Conversely, at the end of a surgical procedure, ZuraPrep™ may not be completely washed off. The secondary endpoint at 6 hours supports continued efficacy of the product after the completion of surgical procedures. Continued efficacy at this point may help prevent SSIs.

7.1.3. Subpopulations

The distribution of nonresponders for the abdomen and groin at 10 minutes post application were similar for ZuraPrep™ and ChloraPrep® across sex, race, and age in both pivotal studies (ZX-ZP-0073, ZX-ZP-0074).

Table 15
Nonresponders, 10 minutes, Abdomen, ZX-ZP-0073/0074

	Number of Nonresponders at 10 Minutes by Sex, Race, and Age (Abdomen, Studies ZX-ZP-0073 and ZX-ZP-0074)						
	Sex		Race		Age (years)		
Study	Female	Male	Caucasian	Other	18-<40	40-<65	≥65
ZX-ZP-0073							
ZuraPrep™	2	10	3	9	7	5	0
ChloraPrep®	0	11	5	6	7	4	0
ZX-ZP-0074							
ZuraPrep™	13	49	59	3	36	20	6
ChloraPrep®	14	52	58	8	37	22	7

Table 16
Nonresponders, 10 minutes, Groin, ZX-ZP-0073/0074

	Number of Nonresponders at 10 Minutes by Sex, Race, and Age (Groin, Studies ZX-ZP-0073 and ZX-ZP-0074)						
	Sex		Race		Age (years)		
Study	Female	Male	Caucasian	Other	18-<40	40-<65	≥65
ZX-ZP-0073							
ZuraPrep™	6	18	11	13	11	12	1
ChloraPrep®	10	19	9	20	11	17	1
ZX-ZP-0074							
ZuraPrep™	19	66	73	12	55	22	8
ChloraPrep®	21	76	86	11	59	31	7

Adapted from Tables 20 and 21, ISE, pages 57-58

7.1.4. Dose and Dose-Response

ZuraPrep™ provides the immediate, broad antiseptic action required of a preoperative skin preparation product, as demonstrated in pivotal studies (ZX-ZP-0073, ZX-ZP-0074).

ZuraPrep™ excipients have been shown to have no therapeutic antiseptic action, as shown in Study ZX-ZP-0068 and in vitro time-kill Study 130548-201. A total application volume of 10.5 mL provides adequate coverage of the surgical area and is consistent with the application volume of the active control (ChloraPrep®) used in the clinical studies of ZuraPrep™ The efficacy of ZuraPrep™10.5 mL was demonstrated in accordance with the procedures outlined in the 1994 TFM, the 2015 Amendment to TFM, the ASTM International methodology standards, and the December 2017 Final Rule (FDA, 2017).

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Persistence of efficacy beyond 6 hours and tolerance effects were studied for this single, topical application in pilot Study ZX-ZP-0035. The study demonstrated persistence at 12 and 24 hours post application for both abdominal and groin test sites, keeping microbial counts reduced over the course of the 24-hour test period.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Efficacy for ZuraPrep™was not determined by clinical outcomes measures, such as reductions in rates of SSIs. Causes of SSIs are often times multifactorial and associating SSIs with the failure or lack of efficacy of specific pre-surgical antimicrobial product would be difficult. Postmarketing reports will focus on AEs associated with the use of ZuraPrep™ and likely not reflect deficiencies in efficacy as it relates to clinical outcomes such as SSIs.

7.2.2. Other Relevant Benefits

ZuraPrep™ is packaged in a 10.5 mL applicator meant for one time use to topically apply ZuraPrep™ to dry intact skin prior to the start of a surgical procedure. The amount of ZuraPrep™ in (1 or 2) applicator(s) is sufficient to cover the surface area on the skin for most surgical procedures. Use of the 10.5 mL applicator will deliver a more consistent amount of ZuraPrep™ compared to a separately packaged antimicrobial topical product applied with a separately packaged swab/sponge/applicator. As such, the antimicrobial activity of ZuraPrep™ in the prepackaged 10.5 mL applicator will also be more consistent.

7.3. Integrated Assessment of Effectiveness

The use of topical antiseptics on surgical sites prior to surgery is widely recognized as a crucial step in preventing SSIs[9]. To that end ZuraPrep™'s effectiveness has been established based on its antimicrobial activity in clinical and in-vitro settings demonstrating that its antimicrobial activity meets the benchmarks established by

[9] Berríos-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surg.* 2017;152(8):784–791. doi:10.1001/jamasurg.2017.0904

applicable TFM, Final Rule and other FDA guidances. Efficacy at 10 minutes post application was the primary endpoint, and both pivotal studies (ZX-ZP-0073, ZX-ZP-0074) demonstrated that ZuraPrep™'s ATEs and responder rates met the required benchmarks at that 10 minutes post application and were favorable compared to the RLD, ChloraPrep® . In addition, ZuraPrepTM also met secondary endpoint ATEs and responder rates at 30 seconds and 6 hours post application.

8. Review of Safety

8.1. Safety Review Approach

As ZuraPrep™ is intended for topical use only, this safety review focused on skin related AEs that might occur over areas of the body where it is applied. The sponsor submitted the following studies to support the safety of ZuraPrep™:

- Pivotal efficacy and safety studies (ZX-ZP-0073 and ZX-ZP-0074)
- Pilot efficacy and safety studies (ZX-ZP-0035, ZX-ZP-0055, and ZX-ZP-0068)
- Phototoxicity studies (ZX-ZP-0016)
- Cumulative irritation studies (Study ZX-ZP-0017)
- Contact sensitization study (Study ZX-ZP-0018)
- Photosensitization (ZX-ZP-0019)
- Skin area covered and dry time (ZX-ZP-0083)

As discussed in section 3.2, after the NDA was submitted, the FDA determined that the proprietary name ZuraPrep™ was unacceptable (b) (4) (b) (4) The FDA directed the sponsor to change the name and the sponsor changed the name to ZuraGard. Another safety issue that was evaluated was the use of MB as an excipient. Case reports are found in medical literature of skin necrosis and other skin reactions associated with injection of MB dye to identify sentinel lymph nodes for surgical procedures[10]. After review, the risk of skin necrosis occurring with ZuraPrep™ due to MB, when used as intended topically on dry intact skin, would be negligible and not warrant mitigation, safety holds or labeling modifications. Details of this issue will be discussed later in this review.

[10] Lee JH, Chang CH, Park CH, Kim JK. Methylene blue dye-induced skin necrosis in immediate breast reconstruction: evaluation and management. *Arch Plast Surg*. 2014;41(3):258-63.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

- 1500 subjects had ZuraPrep™ applied to at least 1 test site
- 1369 subjects were exposed to the reference product, ChloraPrep®
- 660 were exposed to the ZuraPrep™ Vehicle
- 312 were exposed to Normal Saline
- 40 were exposed to sodium lauryl sulfate.

Table 17
Extent of Exposure Across the ZuraPrep™ Clinical Program

	N				
Study# ZX-ZP-XXXX	ZuraPrep™	ChloraPrep®	ZuraPrep™ Vehicle	Normal Saline	Sodium Lauryl Sulfate
0016	34	-	34	-	-
0017	40	40	40	40	40
0018	225	225	225	225	-
0019	55	-	55	-	-
0035	59	32	52	-	-
0055	36	36	-	-	-
0068	42	46	43	47	-
0068 Neutralization[a]	3	3	3	-	-
0073	400[b]	400[b]	80	-	-
0073 Neutralization[a]	6	6	6	-	-
0074	589	590	131	-	-
0074 Neutralization[a]	18	18	18	-	-
0083	20	-	-	-	-
Total	1527	1396	687	312	40
Total-Neutralization	1500	1369	660	312	40

a - Neutralization studies performed to assure that the neutralizers used in the recovery medium quenched the antimicrobial activity of the test products, and were not toxic to the bacteria. None of the subjects in the neutralization studies experienced any adverse events and are excluded from further presentation of safety data.
b - Includes 1 subject who was treated twice in Study ZX-ZP-0073 (Subject (b) (6)); this subject is counted as 2 separate exposures.

Adapted from Table 2, ISS, page 20

Overall, it appears that a sufficient number of subjects were used in the studies to generate data to support the safety of ZuraPrep™.

Efficacy studies, phototoxicity study, and skin area covered and dry time study had exposure periods of less than 24 hours in order to assess for more immediate effects of a single use of ZuraPrep™.

In cumulative irritation, contact sensitization, and photosensitization studies, the exposure periods were at least 21 days, as AEs due to these causes are more likely to appear several weeks after exposure to ZuraPrep™. In the contact sensitization study, ZuraPrep™ 0.02 mL was applied 3 times weekly for 3 weeks, followed by a 14-day Rest Period, and applied again to test sites for a 48-hour Challenge Phase. In the photosensitization study, ZuraPrep™ 0.2 mL was applied to test sites and exposed to irradiation approximately 24 hours later and were performed twice weekly over a 3-week Induction Phase, followed by a 13 to 17-day Rest Period, and applied again to test sites for a 24-hour Challenge Phase.

8.2.2. Relevant characteristics of the safety population:

Across the ZuraPrep™ clinical program, subjects ranged in age from 18 to 85 years, with mean/median ages ranging from 24 to 53.1 years among the studies. The majority of subjects in the pilot and pivotal efficacy studies, as well as the skin area covered/dry time study were male (range: 55.6% to 100%), whereas the majority of the subjects in the dermal reaction studies were female (range: 62.2% to 82.4%). Subjects were predominantly Caucasian in 8 of the 10 studies (range: 40.0% to 100%), and primarily Asian in the remaining 2 studies (43.8% and 45.0%). The majority of the subjects in each of the studies were not of Hispanic or Latino ethnic origin (range: 81.8% to 100%). The sponsor provided the following table summarizing the demographics of ZuraPrep™ clinical program study subjects. See table 18 on the next page.

Table 18
ZuraPrep™ Program Demographics

	Studies									
	ZX-ZP-0016	ZX-ZP-0017	ZX-ZP-0018	ZX-ZP-0019	ZX-ZP-0035	ZX-ZP-0055	ZX-ZP-0068	ZX-ZP-0073	ZX-ZP-0074	ZX-ZP-0083
	(N=34)	(N=40)	(N=225)	(N=55)	(N=64)	(N=36)	(N=89)	(N=440)	(N=640)	(N=20)
Age (Years)										
Mean (SD)	53.1 (10.99)	49[a]	35[a]	50.1 (14.03)	24[a]	35.7 (14.73)	38.9 (14.31)	38.4 (15.32)	30[a]	35.4 (16.55)
Range	24, 75	19, 67	18, 82	18, 74	18, 74	20, 67	19, 75	18, 80	18, 85	20, 77
Sex, n (%)										
Male	6 (17.6)	8 (20.0)	85 (37.8)	11 (20.0)	47 (73.4)	20 (55.6)	57 (64.0)	250 (56.8)	476 (74.4)	20 (100)
Female	28 (82.4)	32 (80.0)	140 (62.2)	44 (80.0)	17 (26.6)	16 (44.4)	32 (36.0)	190 (43.2)	164 (25.6)	0
Race, n (%)										
Asian	2 (5.9)	0	7 (3.1)	0	2 (3.1)	10 (27.8)	39 (43.8)	119 (27.1)	8 (1.3)	9 (45.0)
Black	0	0	4 (1.8)	0	1 (1.6)	2 (5.6)	12 (13.5)	84 (19.1)	9 (1.4)	1 (5.0)
Caucasian	32 (94.1)	39 (97.5)	204 (90.7)	55 (100)	52 (81.3)	20 (55.6)	30 (33.7)	176 (40.0)	576 (90.0)	8 (40.0)
Other or not provided[b]	0	1 (2.5)	10 (4.4)	0	9 (14.2)	4 (11.1)	8 (9.0)	61 (13.9)	47 (7.3)	2 (10.0)
Ethnicity, n (%)										
Not Hispanic/ Latino	34 (100)	39[b] (97.5)	219[b] (97.3)	45 (81.8)	58[b] (90.6)	34[b] (94.4)	82[b] (92.1)	395[b] (89.8)	581 (90.8)	19[b] (95.0)

Abbreviations: SD = standard deviation
[a] Median age.
[b] Ethnicity was captured as race in Study ZX-ZP-0017, Study ZX-ZP-0018, Study ZX-ZP-0035, Study ZX-ZP-0055, Study ZX-ZP-0068, Study ZX-ZP-0073, and Study ZX-ZP-0083 and is included with "Other".

Taken from ISS, page 25

8.2.3. Adequacy of the safety database:

The study population appears to have been sufficiently large and diverse to represent the expected target population. The pivotal studies' methods met the criteria for maximal human exposure outlined in the TFM for Effectiveness Testing of a Patient Preoperative Skin Preparation (FR 59:116, 17 June 94, pp. 31450-31452).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No major issues related to the data integrity and submission quality of this NDA were identified. Information was submitted and organized in the standard eCTD format allowing for substantive review of this NDA. The observations noted below do not impact the reliability of the data reviewed.

The pivotal safety and efficacy study ZX-ZP-0073 and the pilot study ZX-ZP-0055 are notable for the absence of AEs and skin irritation in its safety population. Both of these studies were conducted at the study site by the same primary investigator in Sterling, Virginia.

In contrast, study ZX-ZP-0074 reported 7 AEs in its safety population, with irritation scores showing only erythema for ZuraPrep™, ChloraPrep® and vehicle at 30 seconds, 10 minutes, and 6 hours for both the abdominal and groin sites as shown below.

Table 19
Irritation Scores, Groin, ZX-ZP-0074
Groin

Erythema	ZuraPrep™	ChloraPrep®	Vehicle
Baseline			
0 – No Reaction	441 (100.%)	441 (100.%)	441 (100.%)
1 – Mild/transient redness	0	0	0
2 – Moderate redness	0	0	0
3 – Severe redness	0	0	0
30 seconds			
0 – No Reaction	214 (48.53%)	147 (33.33%)	24 (27.27%)
1 – Mild/transient redness	220 (49.89%)	287 (65.08%)	60 (68.18%)
2 – Moderate redness	7 (1.59%)	7 (1.59%)	4 (4.55%)
3 – Severe redness	0	0	0
10 minutes			
0 – No Reaction	374 (84.81%)	317 (71.88%)	65 (73.86%)
1 – Mild/transient redness	67 (15.19%)	123 (27.89%)	23 (26.14%)
2 – Moderate redness	0	1 (0.23%)	0
3 – Severe redness	0	0	0
6 hours			
0 – No Reaction	429 (97.28%)	430 (97.51%)	85 (96.59%)
1 – Mild/transient redness	12 (2.72%)	11 (2.49%)	3 (3.41%)
2 – Moderate redness	0	0	0
3 – Severe redness	0	0	0

Adapted from table 23(Groin), ZX-ZP-0074, page 71

Table 20
Irritation Scores, Abdomen, ZX-ZP-0074
Abdomen

Erythema	ZuraPrep™	ChloraPrep®	Vehicle
Baseline			
0 – No Reaction	519 (100.0%)	520 (100.0%)	104 (100.0%)
1 – Mild/transient redness	0	0	0
2 – Moderate redness	0	0	0
3 – Severe redness	0	0	0
30 seconds			
0 – No Reaction	373 (71.87%)	301 (57.88%)	58 (56.31%)
1 – Mild/transient redness	143 (27.55%)	218 (41.92%)	45 (43.69%)
2 – Moderate redness	3 (0.58%)	1 (0.19%)	0
3 – Severe redness	0	0	0
10 minutes			
0 – No Reaction	458 (88.25%)	434 (83.46%)	88 (85.44%)
1 – Mild/transient redness	61 (11.75%)	86 (16.54%)	15 (14.56%)
2 – Moderate redness	0	0	0
3 – Severe redness	0	0	0

6 hours 0 – No Reaction 1 – Mild/transient redness 2 – Moderate redness 3 – Severe redness	 504 (97.30%) 13 (2.51%) 1 (0.19%) 0	 498 (95.95%) 20 (3.85%) 1 (0.19%) 0	 99 (96.12%) 4 (3.88%) 0 0

Adapted from table 24 (Abdomen), ZX-ZP-0074, page 73

A review of submitted CRFs for **pivotal studies** indicated that subjects were evaluated appropriately utilizing the same irritation rating system for the studies as per protocol. No CRFs for the **pilot study** were submitted with the NDA as there were no AEs reported but were available on request. Exclusion criteria for these studies were well defined and comparable to each other. Criteria focused on excluding subjects with prior existing skin conditions or exposures that might increase the risk of AEs after topical application of the study drugs. Inclusion criteria focused on including generally healthy adult subjects. The absence and low number of AEs for the respective studies is not unexpected considering the inclusion and exclusion criteria used.

8.3.2. Categorization of Adverse Events

Adverse, serious adverse and treatment-related AEs were well defined for all studies, as were protocols for reporting, treatment and follow up. Anticipated reactions were related to the application of the test materials to the skin. The sponsor included the following anticipated reactions: mild abrasion, adhesive reactions, irritation, erythema, swelling, itching, peeling, and in rare cases blistering or allergic reactions. Irritation was measured with well-defined parameters that included erythema, edema, and rash. AEs for the safety population were reported in verbatim terms instead of MedDRA coding. Due to the low acuity and low number of AEs in the safety population, the absence of MedDRA reporting did not impact this review.

8.3.3. Routine Clinical Tests

Clinical testing for this product focused on the sampling of skin of study subjects for bacteria. Sampling of skin from the groin and abdominal areas of subjects was done using the Cylinder Sampling (Scrub Cup) Technique for the pilot and pivotal studies. Sampling for the pivotal studies was done at baseline before application of study drugs and at various time points after application (30 seconds, 10 minutes and 6 hours). For the pilot study sampling was done after application of drug at 10 minutes only. Antimicrobial efficacy of the study drug and controls were evaluated based upon calculations of mean $\log_{10}$ reductions from baseline populations by subtracting the $\log_{10}$ number of viable microorganisms recovered at each post-product application sample from the $\log_{10}$ number of viable microorganisms recovered in the baseline samples. For pivotal studies, prior to sampling, sites on the abdomen and groin were prepared and marked using sterile templates of predetermined sizes. 5" x 5" for the abdomen and 1.5" x 5" for the groin. Throughout the process of sampling, investigators also continuously looked for signs of skin irritation or more serious skin reactions. The same skin irritation scoring methods

were utilized for the pilot study and both pivotal studies. Sampling and testing procedures were consistent with procedures outlined in the FDA TFM for Health-Care Antiseptic Drug Products (vol. 59, No. 116, June17, 1994, pp. 31450-31452) and ASTM E1173 – 15 Evaluation of Preoperative, Precatheterization, or Preinjection Skin Preparations. No safety concerns noted in regards to clinical testing.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in studies conducted as part of the ZuraPrep™ clinical program.

8.4.2. Serious Adverse Events

The sponsor reported 4 serious AEs during the ZuraPrep™ clinical program, none of which occurred during pivotal studies and none related to test products. Summaries of events as per CRF narratives are as follows:

Study ZX-ZP-0018 Subject (b) (6): 45-year-old Caucasian female who stated that a dog had knocked her over, resulting in a broken leg. The subject was admitted to the hospital for surgery, administered anti-inflammatory and pain medication, and discontinued from the study. The event was considered not related to test products and was noted as resolved during follow-up.

Study ZX-ZP-0019 Subject (b) (6): 24-year-old Caucasian male who was hospitalized with appendicitis. He underwent an appendectomy and was discontinued from the study. The event was considered severe, not related to test products, and was noted as resolved during follow-up.

Study ZX-ZP-0019 Subject (b) (6): 54-year-old Caucasian female who experienced a shoulder muscle strain. The subject received anti-inflammatory, muscle relaxant and pain medication as treatment. As these medications were prohibited by the protocol, the subject was withdrawn from study treatment. The event was considered severe, not related to test products, and was noted as resolved during follow-up.

Study ZX-ZP-0017 Subject (b) (6): 49-year-old Caucasian female developed sinus problems and sore throat that was later diagnosed as tonsillitis. The subject was treated with antibiotics and was discontinued from the study. The event was considered mild, not related to test product, and resulted in discontinuation from the study.

As noted in summaries, these AEs do not appear to have been related to the test products.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

4 subjects discontinued as described in 8.4.2.

8.4.4. Significant Adverse Events

No AEs were reported in ZX-ZP-0016, ZX-ZP-0055, ZX-ZP -0068, ZX-ZP-0073, or ZX-ZP-0083. Most of the significant AEs that occurred in other studies were considered to be mild in intensity, with the exception of the following: four subjects had treatment-emergent AEs that were considered moderate or severe in intensity including moderate flu-like illness (Study ZX-ZP-0018 Subject (b) (6)), moderate diarrhea (Study ZX-ZP-0019 Subject (b) (6)), severe appendicitis (Study ZX-ZP-0019 Subject (b) (6)), and severe shoulder muscle strain (Study ZX-ZP-0019 Subject (b) (6) An additional subject ((b) (6)) in Study ZX-ZP-0018 had a serious treatment-emergent AE of broken leg that did not have intensity indicated on the AE form. For purposes of this review, these AEs appear unrelated to test products as the sponsor has contended.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Across the ZuraPrep™ clinical program, the percentage of subjects with at least 1 treatment-emergent AE was 1.9% for ZuraPrep™. A summary of treatment-emergent AEs reported across the ZuraPrep™ clinical program is presented in the following table.

Table 21
Treatment-emergent Adverse Events Across the ZuraPrep™ Clinical Program

Adverse Event Verbatim Term, n (%)	ZuraPrep™ (N=1500)	ChloraPrep® (N=1369)	ZuraPrep™ Vehicle (N=660)	Normal Saline (N=312)	Sodium Lauryl Sulfate (N=40)
At least 1 adverse event	28 (1.9)	23 (1.7)	21 (3.2)	19 (6.1)	4 (10.0)
Sniffly/Nasal discharge/Stuffy nose/Stuffy, runny nose	4 (0.3)	4 (0.3)	4 (0.6)	4 (1.3)	1 (2.5)
Rash	3 (0.2)	3 (0.2)	1 (0.2)	1 (0.3)	0
Cut	2 (0.1)	0	0	0	0
Nausea/Upset stomach	2 (0.1)	2 (0.1)	2 (0.3)	2 (0.6)	1 (2.5)
Stomach flu/Flu-like illness	2 (0.1)	2 (0.1)	2 (0.3)	2 (0.6)	0
Appendicitis	1 (0.1)	0	1 (0.2)	0	0
Back pain	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Broken leg	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Broken toe	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Contact dermatitis	1 (0.1)	1 (0.1)	0	0	0
Diarrhea	1 (0.1)	0	1 (0.2)	0	0
Fatigue	1 (0.1)	1 (0.1)	0	0	0

Fever	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Folliculitis	1 (0.1)	1 (0.1)	0	0	0
Headache	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Hip pain	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Illness, cold	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Irritation	1 (0.1)	1 (0.1)	0	0	0
Itching/Itchy eyes and back	1 (0.1)	2 (0.1)	1 (0.2)	2 (0.6)	0
Lightheaded	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	1 (2.5)
Neck pain	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Scratch	1 (0.1)	0	0	0	0
Shaky	1 (0.1)	1 (0.1)	1 (0.2)	0	0
Shoulder muscle strain	1 (0.1)	0	1 (0.2)	0	0
Sneezing	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	0
Sore throat	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	1 (2.5)
Tonsillitis	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	1 (2.5)
Burning	0	0	0	1 (0.3)	0

Adapted from Table 5, ISS, page 28

Most events were reported in the cumulative irritation (Study ZX-ZP-0017), contact sensitization (Study ZX-ZP-0018), and photosensitization (Study ZX-ZP-0019) studies, where the exposure periods were at least 21 days (28 of 35 events for ZuraPrep™; 80.0%). The incidences of specific verbatim terms were all <1.0% for ZuraPrep™.

6 subjects had treatment-emergent AEs that were considered by the investigator to have a possible, probable or definite relationship to test products. The related events were associated with the test product application sites and included 2 subjects with rash, 2 subjects with itching, 1 subject with cut, and 1 subject with irritation, folliculitis, and contact dermatitis. Review of the associated CRFs indicate that these events may have been related to test products but were mild in nature and all resolved.

The efficacy studies had an exposure period of 24 hours or less and test products were used per intended application. Across the efficacy studies, the percentages of subjects with at least 1 treatment-emergent AE was <1% for all test products. This is summarized in table 22, next page.

Table 22
Treatment-emergent Adverse Events in ZuraPrep™ Studies Where Test Products Were Used Per Intended Application

Adverse Event Verbatim Term, n (%)	ZuraPrep™ (N=1126)	ChloraPre® (N=1104)	ZuraPrep™ Vehicle (N=306)	Normal Saline (N=47)
At least 1 adverse event	7 (0.6)	4 (0.4)	1 (0.3)	0
Cut	2 (0.2)	0	0	0
Rash	2 (0.2)	2 (0.2)	0	0
Scratch	1 (0.1)	0	0	0
Fatigue	1 (0.1)	1 (0.1)	0	0
Shaky	1 (0.1)	1 (0.1)	1 (0.3)	0

Adapted from Table 6, ISS, page 29

TEAEs for ZuraPrep™ do not warrant inclusion in drug facts labeling based on submitted studies as these events were low in number and acuity. The FDA issued a Drug Safety Communication in February 2017 for the RLD, ChloraPrep that warned of rare but serious allergic reactions have been reported with the widely used skin antiseptic products containing chlorhexidine gluconate. As a result the manufacturers of OTC antiseptic products containing chlorhexidine gluconate were requested by the FDA to add a warning about this risk to the Drug Facts labels. As ZuraPrep™ does not contain chlorhexidine, a similar warning is not warranted for ZuraPrep™.

8.4.6. Laboratory Findings

Evaluations of clinical laboratory values were not performed in studies conducted as part of the ZuraPrep™ clinical program.

8.4.7. Vital Signs

Vital signs, physical findings, and observations other than treatment site assessments were not applicable to review of this NDA.

8.4.8. Electrocardiograms (ECGs)

ECGs were not applicable to review of this NDA.

8.4.9. QT

QT clinical trials not conducted for this NDA and not applicable to review of this NDA.

8.4.10. Immunogenicity

A contact sensitization study (ZX-ZP-0018) and a photosensitization study (ZX-ZP-0019) indicated that ZuraPrep™ had a low risk for causing sensitization. No other direct immunogenicity testing was done as part of this NDA submission.

8.5. Specific Safety Studies/Clinical Trials

In addition to pilot and pivotal studies, this NDA included safety related studies evaluating other potential adverse skin reactions. For these studies, dermal reactions at the test sites were evaluated using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation depending on the type of study conducted.

Phototoxicity (ZX-ZP-0016)

Study ZX-ZP-0016 was a single-center, controlled, randomized, within-subject comparison study of ZuraPrep™ and ZuraPrep™ Vehicle under occlusive patch conditions. An untreated patch served as a negative control. The objective of this study was to determine the irritation potential of ZuraPrep™ and ZuraPrep™ Vehicle when topical application to skin was followed by light exposure. Results of study indicated that the irradiated sites treated with ZuraPrep™ or ZuraPrep™ Vehicle did not react more to UV light than did the irradiated untreated control sites. While irradiation was associated with a dermal response on all sites (ZuraPrep™, ZuraPrep™ Vehicle, Untreated), there was no statistically significant difference in irritation between sites that received irradiation. The FDA Division of Dermatology and Dental Products (DDDP) review of this study determined that it was reasonable to conclude that ZuraPrep™ does not have the potential for phototoxicity. The risk for phototoxicity with use of ZuraPrep™ appears to be low.

Cumulative Irritation (ZX-ZP-0017)

Study ZX-ZP-0017 was a single-center, controlled, randomized, within-subject comparison study of ZuraPrep™, ZuraPrep™ Vehicle, ChloraPrep® (reference product), 0.1% Sodium Lauryl Sulfate (positive control), and 0.9% Physiological Saline (negative control) under occlusive patch conditions. The objective of this study was to determine the skin irritation potential of ZuraPrep™ and ZuraPrep™ Vehicle after repetitive patch applications over a 21 day period. The mean irritation score of exposed sites to ZuraPrep™ showed that it was greater than the ZuraPrep™ Vehicle and the Sodium Lauryl Sulfate (positive control), but less than sites exposed to the ChloraPrep® after 21 days of exposure. This was a standalone cumulative irritation study that compared the irritation potential of ZuraPrep™, vehicle, reference product, positive control, and negative control. The DDDP determined that overall, ZuraPrep™ was shown to have irritation potential under the study's provocative conditions.

Contact Sensitization (ZX-ZP-0018)

Study ZX-ZP-0018 was conducted to determine the allergic contact sensitization potential of ZuraPrep™ and the ZuraPrep™ Vehicle after repetitive patch applications to the skin of human subjects. ChloraPrep® and 0.9% Physiological Saline were employed as a reference product and negative control, respectively. The study was conducted in 3 phases: Induction, Rest, and Challenge. A total of 225 subjects were treated with test products, and 208 subjects completed all phases of testing with their respective data used in the primary analysis for evaluation of sensitization. Of the 208 subjects who completed testing, 1 displayed sensitizing characteristics related to ZuraPrep™ and ChloraPrep®. Additionally, 1 subject showed a potential sensitivity to ChloraPrep®, although irritation was also a likely possibility for this case. Seven subjects displayed more mild signs of possible sensitization escalating in irritation scores of 2 to 3 at 72 hours (2 related to ZuraPrep™, 3 related to ChloraPrep® , and 2 related to 0.9% Physiological Saline). Based on these results, ZuraPrep™ has the potential to cause sensitization.

Photosensitization (ZX-ZP-0019)

Study ZX-ZP-0019 was a single-center, controlled, randomized, within-subject comparison study of ZuraPrep™ and ZuraPrep™ Vehicle under occlusive patch conditions. An untreated patch served as a negative control. The objective of this study was to determine the ability of ZuraPrep™ and ZuraPrep™ Vehicle to induce a photoallergic skin reaction using a controlled photopatch testing procedure. These procedures were performed twice weekly over a 3-week Induction Phase (6 applications/irradiation). The sites were examined at various time points for the purpose of determining photoallergic skin reactions. At the end of the Induction Phase, the subjects entered a Rest Period of 13-17 days, followed by a Challenge Phase. All sites were examined for dermal reactions at approximately 24, 48, and 72 hours post irradiation. During the Induction Phase, most of the reactions were Grade 1 irritation (mild but definite erythema), but some Grade 2 irritation (moderate erythema or mild but definite erythema plus mild but definite edema) was noted at some sites in all treatment groups. There was statistically significantly more irritation at the irradiated ZuraPrep™ sites than at the irradiated vehicle and irradiated untreated sites ($p<0.0001$), likely attributable to the presence of the active ingredient, IPA as there were no statistically significant differences in irritation between the vehicle and untreated sites. During Challenge, the maximum response observed among the subjects was Grade 1 irritation, which was noted at some irradiated sites for each of the 3 treatments as well as some non-irradiated ZuraPrep™ sites. No irritation was noted at any non-irradiated vehicle or untreated sites. The FDA DDDP review of this study determined that it was reasonable to conclude that ZuraPrep™ does not have the potential for photosensitization. The risk for photosensitization with use of ZuraPrep™ appears to be low.

Skin Coverage and Dry Time (ZX-ZP-0083)

Study ZX-ZP-0083 was a single-center, open-label treatment design where each subject received a single topical application of ZuraPrep™. The objective of this study was to measure the proposed coverage area and dry time of a single ZuraPrep™ applicator. A single 10.5 mL applicator of ZuraPrep™ was applied for 30 seconds over a 8.4" × 8.4" area on the subject's back and allowed to air dry. The dose administered was determined by calculating the difference in the pre-treatment and post-treatment investigational product weight (g), including packaging. Results are summarized in table below.

Table 23
Skin Coverage and Dry Time ZX-ZP-0083

	Excluding outlier				Including outlier			
	Coverage Area Dose (g/cm^2)	Dry Time (sec)	Dose (g)	Coverage per Dose (cm^2/g)	Coverage Area Dose (g/cm^2)	Dry Time (sec)	Dose (g)	Coverage per Dose (cm^2/g)
Mean	0.00567	100.2	2.58	178	0.00560	103.5	2.55	180
Median	0.00584	102.7	2.66	171	0.00569	103.7	2.59	176
Min	0.00474	77.0	2.16	161	0.00442	77.0	2.01	161
Max	0.00622	136.0	2.83	211	0.00622	165.7	2.83	226

Table 8 from ZX-ZP-0083, page 16

The sponsors concluded that ZuraPrep™ that treatment area dry time was in line with class labeling for preoperative antiseptic products. Draft labeling for ZuraPrep™ states: [redacted] solution [redacted] completely dry (minimum of 3 minutes on hairless skin; up to 1 hour in hair). Do not blot or wipe away." Reported dry times over hairless skin were less than 3 minutes. Dry times in hair were not evaluated in this study, but instructions to allow up to an hour to dry after application in hair is consistent with class labeling with other preoperative antiseptic products.

8.6. Additional Safety Explorations

8.6.1. Human Carcinogenicity or Tumor Development

Carcinogenicity and tumor development was not evaluated for this NDA. Exposure to ZuraPrep™ would be brief and episodic when used as a single use topical antiseptic prior to surgical procedures. Carcinogenicity would be less likely with this episodic pattern of use.

8.6.2. Human Reproduction and Pregnancy

ZuraPrep™ studies required that female subjects be unable to become pregnant, or that females of childbearing potential were using acceptable methods of birth control. All female subjects participating in the ZuraPrep™ clinical program were required to have

negative urine pregnancy tests prior to application of test product. Urine pregnancy tests were also required at the end of study in Studies ZX-ZP-0016 and ZX-ZP-0019.

8.6.3. Pediatrics and Assessment of Effects on Growth

None of the studies in the ZuraPrep™ clinical program evaluated pediatric subjects as the FDA agreed that PREA was not triggered for this NDA. However, the proposed drug facts label appropriately states to use with care in premature infants or infants 2 months of age as it may cause irritation or chemical burns, and the possibility of enhanced absorption of the drug due to increased skin permeability due to greater surface area-to-volume ratios in younger infants.

8.6.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no reports of overdose in the ZuraPrep™ clinical program. Preoperative antiseptic products, like ZuraPrep™, are not known for abuse or dependence potential. As none of the ingredients in ZuraPrep™ are controlled substances a CSS consult was not obtained.

8.7. Safety in the Postmarket Setting

8.7.1. Safety Concerns Identified Through Postmarket Experience

No marketing applications for ZuraPrep™ (IPA 70%) solution have been submitted to any country.

8.7.2. Expectations on Safety in the Postmarket Setting

The sponsor included postmarketing data for other products containing IPA from FAERS the World Health Organization Uppsala Monitoring Center VigiBase, and the National Poison Data System. Interpretation of this data is limited as event rates cannot be estimated because the number of treated subjects is not available. Review of data did not reveal concerning safety signals as most databases showed most events were skin related events that might be expected with use.

The National Poison Data System showed that for 2016, 80% of human exposure cases reported were associated with ingestion of IPA products. As expected, these AEs were more serious in nature. The risk for ingestion of ZuraPrep™ when used as intended would be nearly non-existent. The sponsor also included case reports of toxicity following dermal exposure of IPA in medical literature and in the NDA submission. These case reports involved a variety of IPA products used in a variety of settings that did not demonstrate safety signals readily applicable to ZuraPrep™ when used as intended.

8.7.3. Additional Safety Issues From Other Disciplines

As discussed in the introduction, the FDA determined that the proprietary name of ZuraPrep™ was unacceptable (b) (4) (b) (4) (b) (4) (b) (4) In response, the sponsor submitted a new proprietary name of ZuraGard, which is acceptable.

MB is an excipient (b) (4) included in ZuraPrep™ to highlight the coverage area when ZuraPrep™ is applied to skin. A phototoxicity study (ZX-ZP-0016) and a photosensitization study (ZX-ZP-0019) were conducted to show that neither MB, nor the ZuraPrep™ formulation, caused a phototoxic or photoallergic response after repeated irradiation exposures. These studies showed that ZuraPrep™ did not produce either of these responses. A 21-Day Dermal Toxicity Study with ZuraPrep™ in Minipigs (ZX-ZP-003) concluded that daily topical administration of ZuraPrep™ applied for 21 days was well tolerated. Blue discoloration of the skin did occur but was not considered an adverse reaction and not unexpected. MB was minimally absorbed as demonstrated by plasma concentrations that were below the lower limit of quantitation (<0.300 ng/mL). The FDA approved ProvayaBlue® (MB injection, 5 mg/mL, NDA 204630) in April 2016, with indication for the treatment of pediatric and adult patients with acquired methemoglobinemia. Approved labeling for PROVAYBLUE® describes nonclinical safety findings for MB, including positive signals in in vitro and in vivo genetic toxicity studies, oral embryofetal development studies in rats and rabbits, and 2-year oral carcinogenicity studies in rats and mice. Labeling for PROVAYBLUE® identifies MB as a carcinogen and as inducing abortions/malformations. FDA DNDP PharmacologyToxicology (PharmTox) review determined that these data do not appear to be relevant to ZuraPrep™ as MB was not detected circulating in plasma following repeated dermal application in the minipig toxicity study previously discussed above. PharmTox review concluded that the proposed levels of MB did not raise safety concerns from the nonclinical perspective.

Case reports are found in medical literature of skin necrosis and other skin reactions associated with injection of MB dye to identify sentinel lymph nodes for surgical procedures[11]. As MB dye was directly injected into tissue in these case reports, the exposure to MB was significantly different from topical application of ZuraPrep™ on dry intact skin. The risk for serious skin reactions, such as skin necrosis, due to MB appears to be negligible when ZuraPrep™ is used as intended as non-clinical studies did not detect MB

[11] Lee JH, Chang CH, Park CH, Kim JK. Methylene blue dye-induced skin necrosis in immediate breast reconstruction: evaluation and management. Arch Plast Surg. 2014;41(3):258-63.
Reyes F, Noelck M, Valentino C, Grasso-Lebeau L, Lang J. Complications of methylene blue dye in breast surgery: case reports and review of the literature. J Cancer. 2010;2:20-5. Published 2010 Dec 8.
Benjamin Stradling, Gerard Aranha, Sheryl Gabram, Adverse skin lesions after methylene blue injections for sentinel lymph node localization, The American Journal of Surgery, Volume 184, Issue 4, 2002, 350-352.

in plasma in animal studies.

8.8. Integrated Assessment of Safety

ZuraPrep™ is a topically applied antiseptic/antimicrobial drug that is intended to reduce bacteria on the skin immediately prior to surgical procedures in order to reduce the risk of infections. The role of antiseptic/antimicrobial drug products containing IPA is recognized as an important measure in the prevention of hospital acquired infections such as SSIs. The submitted safety studies focused on the risk of adverse skin reactions that might occur with topical application of ZuraPrep™. The studies were appropriately conducted and did not identify any unexpected skin reactions or safety signals. AEs reported from the safety population were low in number and acuity and mostly resolved on their own. The safety profile overall matched or exceeded the safety profile of the RLD (ChloraPrep®) used in the studies. No safety issues or signals were identified that would preclude approval of this NDA for ZuraPrep™.

9. Advisory Committee Meeting and Other External Consultations

Advisory Committee Meeting or other external consultations were not necessary for review of this NDA.

10. Labeling Recommendation

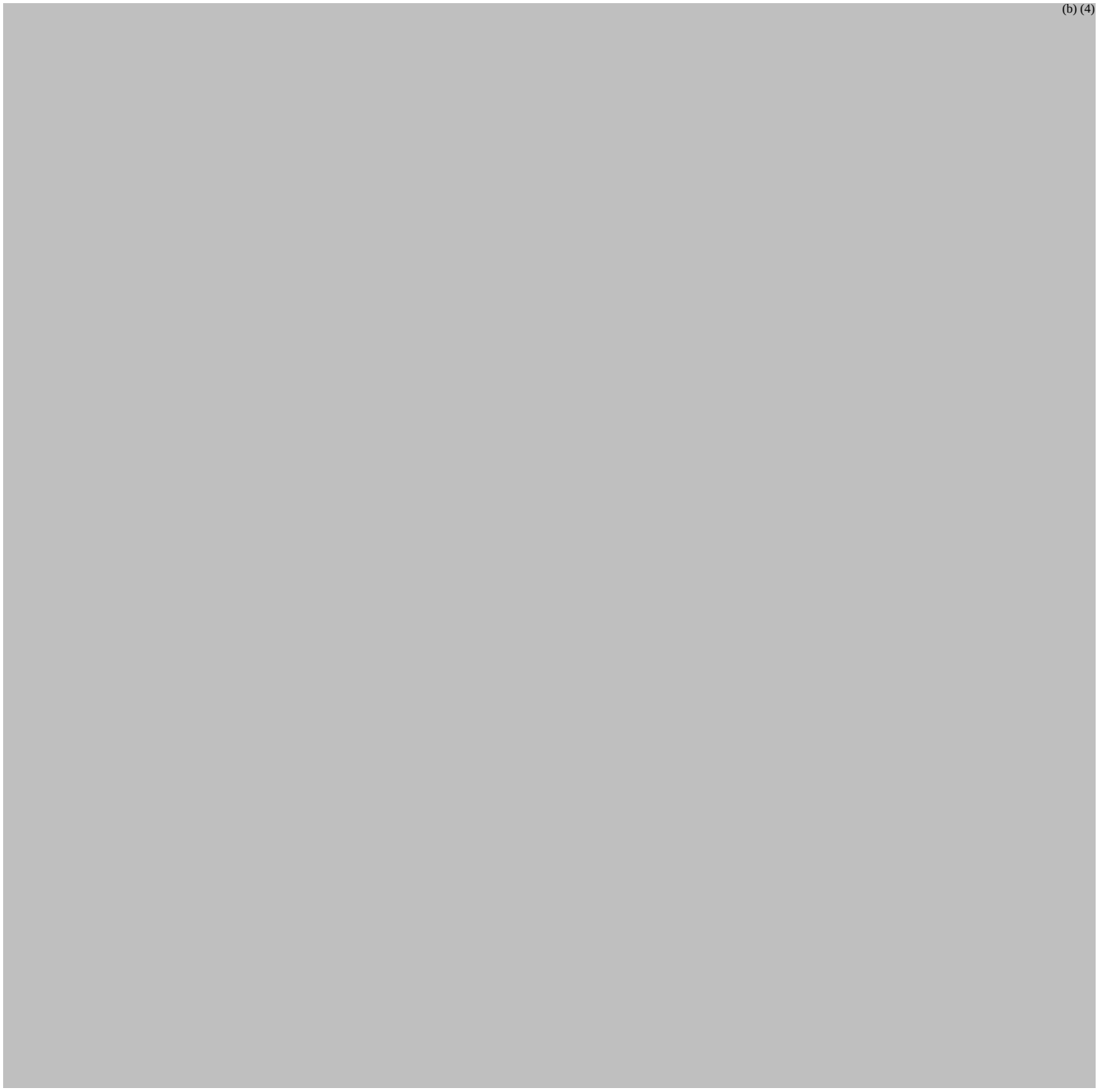
10.1. Prescription Drug Labeling

Not applicable as this NDA is for a Nonprescription Drug Product.

10.2. Nonprescription Drug Labeling

Proposed label:

(b) (4)



As previously discussed, the FDA determined that the proprietary name of ZuraPrep™ was unacceptable (b) (4) (b) (4) The label displays the updated proprietary name of ZuraGard. Indications, warnings and directions are accurate, understandable, and consistent with class labeling of other pre-surgical topical antiseptics.

11. Risk Evaluation and Mitigation Strategies (REMS)

No safety issues requiring REMS were identified.

12. Postmarketing Requirements and Commitments (PMRs/PMCs)

The proprietary name of ZuraPrep™ was identified as a safety issue (b) (4) ZuraPrep™ was changed to ZuraGard™ and does not require PMRs/PMCs. No other safety issues warranting more than routine pharmacovigilance were identified.

13. Appendices

13.1. References

References have been cited in footnotes and with applicable tables and charts.

13.2. Financial Disclosure

Study ZX-ZP-0073: Pivotal Clinical Evaluation of the Antimicrobial Effectiveness of Topically Applied ZuraPrep™

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor:0 Sponsor of covered study: Zurex		
Is an attachment provided with details of the disclosable financial interests/arrangements: **N/A, no investigators with disclosures**	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A – box 3 not checked**	Yes ☐	No ☐ (Request explanation from Applicant)

Study ZX-ZP-0074: Pivotal Clinical Evaluation of ZuraPrep™, A Patient Preoperative Skin Preparation

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 11		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor: 0 Sponsor of covered study: Zurex		
Is an attachment provided with details of the disclosable financial interests/arrangements: **N/A, no investigators with disclosures**	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A – box 3 not checked**	Yes ☐	No ☐ (Request explanation from Applicant)

Study ZX-ZP-0016: A 4-Day, Randomized Study to Evaluate the Irritation Potential of ZuraPrep™™ when Application to Skin is Followed by Light Exposure in Healthy Volunteers, Using a Phototoxicity Patch Test Design

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor:0 Sponsor of covered study: Zurex		
Is an attachment provided with details of the disclosable financial interests/arrangements: **N/A, no investigators with disclosures**	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A, box 3 not checked**	Yes ☐	No ☐ (Request explanation from Applicant)

Study ZX-ZP-0017: A 21-Day Evaluation of the Cumulative Irritation Potential of Topically Applied ZuraPrep™ and ZuraPrep™ Without IPA in Healthy Adult Volunteers

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor: 0 Sponsor of covered study: Zurex		
Is an attachment provided with details of the disclosable financial interests/arrangements: **N/A, no investigators with disclosures**	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A, box 3 not checked**	Yes ☐	No ☐ (Request explanation from Applicant)

Study ZX-ZP-0018:A Clinical Evaluation of the Contact Sensitizing Potential of Topically Applied ZuraPrep™ and ZuraPrep™ Without IPA in Healthy Adult Volunteers

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor: 0 Sponsor of covered study: Zurex		
Is an attachment provided with details of the disclosable financial interests/arrangements: **N/A, no investigators with disclosures**	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A, box 3 not checked**	Yes ☐	No ☐ (Request explanation from Applicant)

Study ZX-ZP-0019: A 6-Week, Randomized Study to Evaluate the Potential of ZuraPrep™ and Vehicle to Induce a Photoallergic Skin Reaction in Healthy Volunteers, Using a Controlled Photopatch Test Design

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor: 0 Sponsor of covered study: Zurex		
Is an attachment provided with details of the disclosable financial interests/arrangements: **N/A, no investigators with disclosures**	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A, box 3 not checked**	Yes ☐	No ☐ (Request explanation from Applicant)

Study ZX-ZP-0083: Evaluation of the Skin Area Covered and Dry Time of a Preoperative Skin Preparation

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor: 0 Sponsor of covered study: Zurex		
Is an attachment provided with details of the disclosable financial interests/arrangements: **N/A, no investigators with disclosures**	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A, box 3 not checked**	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EDWARD H CHIN
03/28/2019 10:56:44 AM

FRANCIS E BECKER
03/28/2019 11:24:51 AM