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E-101 SOLUTION, A NOVEL ANTISEPTIC INTENDED FOR DIRECT APPLICATION WITHIN A SURGICAL WOUND TO PREVENT SURGICAL-SITE INFECTION: BLINDED, CONTROLLED PHASE 1 SKIN-IRRITATION STUDY IN HEALTHY ADULT VOLUNTEERS

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ABSTRACT

Background: Surgical-site infections are common during many surgical procedures and are increasingly caused by highly virulent and multidrug-resistant microorganisms. Currently, no antiseptics are approved for use directly in an open surgical wound to reduce surgical-site infection. E-101 Solution is a novel myeloperoxidase-based antimicrobial product being investigated for use in patients at high risk for surgical-site infection. This Phase 1 study was conducted to ascertain the skin-irritation potential of E-101 Solution in healthy adult volunteers.

Methods: The study involved 4 drugs: E-101 Solution 300 GU/mL, E-101 Solution 100 GU/mL, 0.1% sodium lauryl sulfate, and 0.9% saline. (The amount of porcine myeloperoxidase [p-MPO] in E-101 Solution is expressed in guaiacol units [GU]; this is the amount of peroxidase enzyme that catalyzes the conversion of 1 µmol of hydrogen peroxide per minute at 25°C.) These were applied to 8 abraded and nonabraded skin sites each day during a 21-day study period. Skin irritation was evaluated at each study visit and evaluated cumulatively at the end of the study.

Results: No clinically significant physical examination findings were noted among the study participants. No adverse events, serious adverse events, or adverse patterns evident from laboratory safety testing were noted among the treated participants.

Conclusions: Skin-irritation scores for the E-101 Solutions 100 GU/mL and 300 GU/mL were significantly lower than the 0.1% sodium lauryl sulfate positive control (P<0.05). All E-101 Solution–related skin reactions were resolved completely within 48 hours following the last drug exposure. The results demonstrate that E-101 Solution is not a skin-irritating agent and is safe for application to abraded and nonabraded human skin.

INTRODUCTION

E-101 Solution is a novel antimicrobial agent being developed by Exoxemis, Inc. It is formulated to mimic the host's innate defense against microbes by generating myeloperoxidase end-products. E-101 Solution consists of 2 active ingredients: glucose oxidase, derived from *Aspergillus niger*, and p-MPO. The enzymatic activity of glucose oxidase produces a steady state of hydrogen peroxide that is critical for p-MPO to continuously generate its end-products, hypochlorous acid and singlet oxygen. These myeloperoxidase end-products are extremely efficient in killing microbes on contact.

Figure 1 provides a schematic representation of the reactions occurring in E-101 Solution.

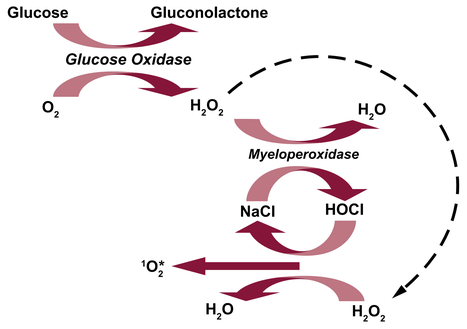
E-101 Solution at low concentration (<4 GU/mL) has been demonstrated in vitro and in vivo in animal microbial challenge models to kill bacteria, fungi, and yeast within seconds to minutes. This broad microbicidal profile has been demonstrated for purified microbe cultures and combinations of microbial cultures. Furthermore, E-101 Solution kills antibiotic-sensitive and antibiotic-/polymicrobial-resistant microorganisms commonly isolated from surgical-site infections, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* sp, *Enterococcus* sp, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and anaerobes (eg, *Bacteroides fragilis*, *Peptostreptococcus* sp, and *Clostridium* sp). Furthermore, it exhibits uniformly effective killing of highly resistant microbes, including methicillin-resistant *S aureus* (MRSA), vancomycin-resistant enterococci (VRE), imipenem-resistant *Acinetobacter* sp, and aerobic gram-negative bacteria resistant to many third-generation beta-lactams and/or highly resistant to high-level aminoglycosides.

Exoxemis plans to develop E-101 Solution as a product that is applied directly into a surgical wound via a microspray. This is based on testing that demonstrates E-101 Solution enhances reepithelialization of deep experimental wounds in a pig model. Good Laboratory Practice safety studies in rats and dogs have determined no safety concerns for E-101 Solution. Currently, there are no myeloperoxidase-based drugs on the market nor any antiseptics approved for use directly in an open surgical wound to reduce surgical-site infection.

Prior to our clinical testing of E-101 Solution in surgical patients at high risk for surgical-site infection (eg, elective colorectal surgery), it is necessary to conduct a series of Phase 1 studies to ascertain the safety of E-101 Solution in healthy adult volunteers. This Phase 1 study summarizes the skin-irritation potential of E-101 Solution.

INTRODUCTION (CONT)

Figure 1. Schematic of glucose oxidase and myeloperoxidase-coupled reactions in E-101 Solution after the addition of glucose substrate.



METHODS

Study Design: Patient-blinded and evaluator-blinded Phase 1 study.

Study Population: Only participants who met all inclusion criteria (eg, male or female; ≥18 years; in good health without any skin abnormalities on the back) and were not rejected by exclusion criteria (eg, pertinent allergies; usage of steroids, antihistamines, or anti-inflammatory agents; chronic medical conditions; pregnancy; drug abuse) were enrolled into this study.

Study Drugs: Four study drugs were evaluated: E-101 Solution 300 GU/mL p-MPO/53.3 GU/mL glucose oxidase; E-101 Solution 100 GU/mL p-MPO/17.8 GU/mL glucose oxidase; 0.1% sodium lauryl sulfate (positive control); 0.9% saline (negative control).

Assessments: Each study drug was assessed on abraded and nonabraded skin during 21 consecutive days. Skin testing comprised 8 skin sites on the upper back; 4 sites randomly abraded only on Day 1, just prior to study agent application using D-SQUAME® Skin Sampling Discs (CuDerm Corporation, Dallas, TX); and 1 abraded skin site and 1 nonabraded skin site randomly selected for each study drug.

Study drugs were applied in direct contact with the skin via a 0.8 cm or 0.5 cm^2 filter paper placed in a Finn Chamber® (SmartPractice, Phoenix, AZ) on Scanpor® (Bard Medical Division, Covington, GA) with 0.02 mL of study agent placed on the filter paper disc per application.

Skin irritation was evaluated at each daily study visit during the 21-day period.

Safety Evaluations: Each participant was evaluated before and after the 21-day study period by physical exam and conventional laboratory testing (ie, complete blood count, coagulation tests, serum chemistry, and urinalysis, inclusive of microscopic evaluation).

Skin Scoring:

Skin irritation scoring scale:
0 No evidence of irritation
1 Minimal erythema
2 Definitive erythema
3 Erythema and papules
4 Definite edema
5 Erythema, edema, and papules
6 Vesicular eruption
7 Strong reaction spreading beyond test site

Any score ≥3 was considered an adverse event. Product application on the site was discontinued and the participant was discontinued from further study drug testing.

Data Analysis: Minitab® Statistical Software (Minitab Inc., State College, PA) was used for all statistical computations. Individual daily visual evaluation scores were provided in a tabular form, as were the percentages of sites with each grade of skin reaction on each study day. The mean skin-irritation scores recorded on each test day and the total cumulative skin-irritation scores were calculated for the study drug test products, the 0.1% sodium lauryl sulfate positive control, and the 0.9% saline USP negative control applied to abraded and nonabraded skin. The values for the test product were compared with those for the positive control and negative control using the Mann-Whitney U Test at a significance level of a = 0.05 (95% confidence level).

RESULTS

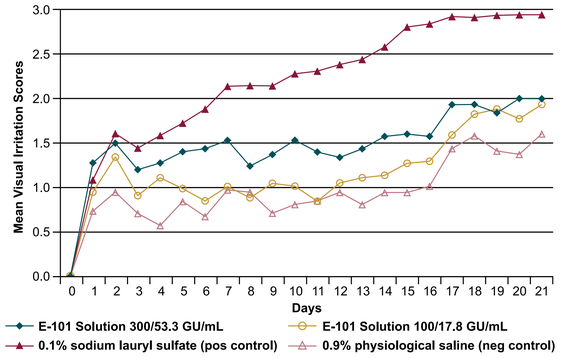
No clinically significant physical examination findings were noted among the subjects. No adverse events, serious adverse events, or adverse patterns evident from laboratory safety testing were noted among the treated subjects.

The graphic presentation of mean visual irritation scores for evaluation of skin irritation after 21 consecutive days for each study drug are presented for abraded skin **(Figure 2)** and nonabraded skin **(Figure 3).**

Table 1 summarizes the mean cumulative skin-irritation score (CSIS) for each of the study drugs among the study population.

Skin-irritation scores from abraded and nonabraded skin were lower in response to E-101 Solution exposure than those of the positive control (P<0.05). It should be noted that all E-101 Solution–related skin reactions were completely resolved within 48 hours following the last drug exposure.

Figure 2. Graphic presentation of mean visual irritation scores for evaluation of skin irritation from 2 test products, positive control, and negative control exposed to abraded skin for 21 consecutive days.



RESULTS (CONT)

Figure 3. Graphic presentation of mean visual irritation scores for evaluation of skin irritation from 2 test products, positive control, and negative control exposed to nonabraded skin for 21 consecutive days.

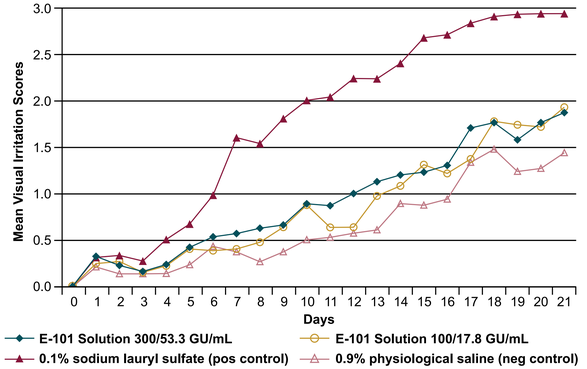


Table 1. Mean Cumulative Skin-Irritation Score (CSIS)

Study Drug	Mean CSIS: Abraded Skin	Mean CSIS: Nonabraded Skin
Physiological saline (negative control)	20.63	13.90
E-101 Solution 100 GU/mL	25.53	18.23
E-101 Solution 300 GU/mL	32.33	20.10
Sodium lauryl sulfate (positive control)	47.60	38.77

CONCLUSIONS

EOE-101 Solution 100/17.8 GU/mL and 300/53.3 GU/mL administered daily for 21 consecutive days produced mild irritation to abraded and nonabraded skin. However, skin-irritation scores were significantly lower than scores for the 0.1% sodium lauryl sulfate positive control (P<0.05). Furthermore, all E-101 Solution–related skin reactions were completely resolved within 48 hours following the last drug exposure.

The results of this conventional, cumulative Phase 1 skin-irritation study demonstrate clearly that E-101 Solution is not a skin-irritating agent and is safe for application to abraded and nonabraded human skin.