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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	209305
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Submission Type	Original NDA (Standard); 505(b)(2)
Applicant	Aclaris Therapeutics Inc.
Submission Date	February 24, 2017
PDUFA Goal Date	December 24, 2017
Brand Name	ESKATA™
Generic Name	Hydrogen Peroxide Topical Solution, 40%
Dosage Form and Strength	Solution, 40%
Route of Administration	Topical
Proposed Indication	Treatment of raised seborrheic keratoses
Proposed Dosage Regimen	To be applied by healthcare providers directly to the targeted lesion(s) up to 4 times, approximately 1 minute apart, during a single in-office treatment session
Primary reviewer	Yanhui Lu, PhD
Secondary reviewer	Chinmay Shukla, PhD
Division Director	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Dermatology and Dental Products/ODEIII

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1 Executive Summary

The Applicant submitted the current NDA for ESKATA [hydrogen peroxide (H_2O_2)] topical solution, 40% for the treatment of raised seborrheic keratoses (SK). The proposed dosage and administration of ESKATA is to be applied directly to the targeted SK lesion(s) up to 4 times, approximately 1 minute apart, during a single in-office treatment session. Hydrogen peroxide is an oxidizing agent commercially available in the United States market at low concentrations (e.g., 3% to 6%) as wound care and disinfectant products despite the unapproved status as a drug by the FDA.

The overall clinical development program comprised a proof-of-concept study in subjects with target SK lesions on the back (A-101-SEBK-201), two Phase 2 dose-ranging studies in subjects with target SK lesions on the trunk/extremities (A-101-SEBK-202) or face (A-101-SEBK-203), two Phase 3 studies (A-101-SEBK-301 and A-101-SEBK-302) with target lesions on the trunk/extremities and face, an open-label safety study (A-101-SEBK-303), and a maximal use trial (A-101-SEBK-205). The strengths of hydrogen peroxide solution investigated during development were 25%, 32.5%, and 40%. The strength of 40% was evaluated in the to-be-marketed formulation in the pivotal Phase 3 clinical studies and in the maximal use trial.

No studies were conducted to evaluate the metabolism and drug-drug interaction potential of the topically applied hydrogen peroxide.

The primary focus of this Question-Based Review is on the assessment of the clinical pharmacology information in the product labeling for ESKATA. The Appendix of this review provides a summary of the maximal use trial.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 3 finds NDA 209305 acceptable pending agreement on recommended labeling changes.

1.2 Post-Marketing Commitments/Requirements

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

1.3.1. Pharmacokinetics

Absorption: Systemic exposure of hydrogen peroxide has not been directly measured. Instead, concentrations of glutathione (GSH, reduced form) and glutathione disulfide (GSSG, oxidized form) in blood were measured; the changes in concentration ratio of GSH to GSSG (referred to as GSH/GSSG in the review below) relative to pre-dose in each subject were calculated to evaluate the systemic absorption of hydrogen peroxide because GSH can be converted to GSSG in the presence of oxidative stress such as hydrogen peroxide. At Visit 2 (no drug applied), the profile of GSH/GSSG ratio during a period of 6 hours was flat; the GSH/GSSG ratios did not change over time. At Visit 3, following a single treatment of ESKATA to ten seborrheic keratosis lesions (with at least one lesion on the face) in patients, the GSH/GSSG ratio in blood samples collected over a period of 6 hours (time points were matched between Visits 2 and 3) did not decrease compared to that of the pre-dose sample collected on the same day

(**Figure 1.3.1**); instead, GSH/GSSG ratio appeared to increase following the treatment of ESKATA although no significant change was observed compared to pre-dose. The observation of no reduction in GSH/GSSG ratio in blood samples from this study suggested lack of systemic absorption of hydrogen peroxide following treatment of ESKATA.

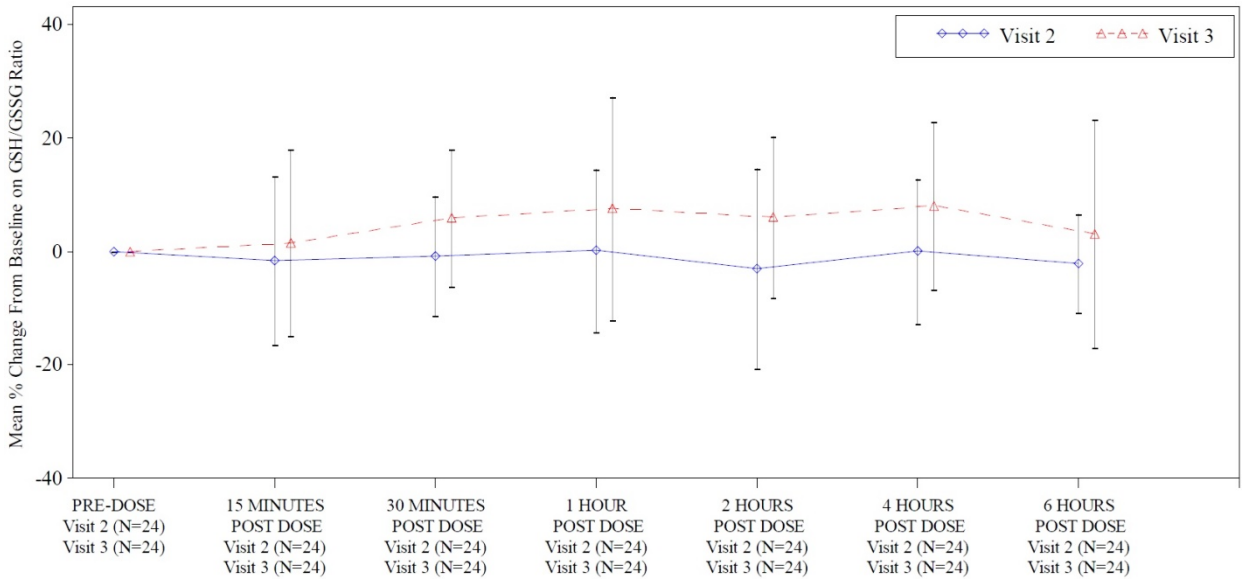

Figure 1.3.1. Mean (standard deviation) % change of GSH/GSSG ratio from baseline at Visits 2 (no treatment) and 3 (ESKATA treatment) in study A-101-SEBK-205. ESKATA was applied to ten seborrheic keratosis lesions (with at least one lesion on the face) in 24 subjects with SK lesions on the trunk, extremities, and face at Visit 3. The first sample was collected at the same time of the day during Visits 2 (no treatment) and 3 (ESKATA treatment). *Source document: Figure 14.2.3 of Study A-101-SEBK-205 tables and figures.*

1.3.2. Pediatrics:

The Applicant requested a full waiver of the requirement to conduct studies in pediatric patients from 0 to 17 years of age. The Agency has agreed to the Applicant's request.

2. Question-Based Review

2.1 General Attributes

2.1.1 What is ESKATA?

ESKATA is a solution that contains 40% (w/w) hydrogen peroxide. The drug product is packaged into a single use hand-held applicator which delivers no less than 0.7 mL (for a 1.5 mL fill) and no less than 1.3 (for a 2.2 mL fill) of drug product solution.

Reviewer comments: *Hydrogen peroxide was not considered as a new molecular entity and the applicant followed a 505(b)(2) regulatory pathway. No relative bioavailability studies were deemed necessary to establish any clinical bridge as there were no signs of in vivo absorption of hydrogen peroxide.*

2.1.2 What is the to-be-marketed formulation/product of ESKATA?

The formulation composition of to-be-marketed ESKATA solution is presented in **Table 2.1.2**.

Table 2.1.2. The formulation composition of ESKATA.

Ingredients	% w/w	Function
Hydrogen Peroxide, (b) (4)	80	Active
Isopropyl Alcohol, USP	(b) (4)	
Sterile Water (b) (4) USP		

2.1.3 What are the proposed indication and dosing regimen for ESKATA?

The proposed indication is for the topical treatment of SK lesions in adults. The proposed dosing regimen is to apply directly to the targeted SK lesion(s) up to 4 times, approximately 1 minute apart, during a single in-office treatment session. ESKATA is administered by healthcare providers and not intended for self-administration by the patients.

2.2 General Clinical Pharmacology

2.2.1 What clinical pharmacology and pivotal clinical trials were used to support the NDA for ESKATA?

Clinical Pharmacology Studies:

The Clinical Pharmacology program of the NDA contains one study conducted under maximal use conditions.

- **A-101-SEBK-205**

  The study assessed the safety and changes of GSH/GSSG in blood following a single treatment of ESKATA in the to-be-marketed formulation to ten seborrheic keratosis lesions (with at least one lesion on the face) in subjects with SK lesions on the trunk, extremities, and face. The changes in concentration ratio of GSH/GSSG in blood were measured as an indicator of changes in the blood concentration of hydrogen peroxide following a single treatment of ESKATA. The Appendix of this review has provided a summary of this study.

Phase 3 Efficacy and Safety Studies:

- **Pivotal Studies A-101-SEBK-301 and A-101-SEBK-302**

  The two pivotal studies with identical study design assessed the safety and efficacy of ESKATA for the treatment of SK by treating four SK target lesions that included at least one lesion on the face and at least one on the trunk or extremities.

- **A long-term safety Study A-101-SEBK-303**

  This study was an open-label study to evaluate the long-term safety of the to-be-marketed formulation of ESKATA.

2.2.2 How was the dose selected for Phase 3?

The hydrogen peroxide concentration of 40% was selected for evaluation in Phase 3 studies based on the results of a proof-of-concept study and two Phase 2 dose-ranging studies.

The proof-of-concept study (A-101-SEBK-201) evaluated hydrogen peroxide solutions at 3 concentrations, 25%, 32.5%, and 40%, and compared the active treatments to vehicle. The 32.5% and 40% concentrations demonstrated statistically significant results in clearing SK lesions while the 25% concentration had marginal to no effect when compared with vehicle (data not shown). Therefore, 25% was determined to be an ineffective concentration and was not evaluated further.

The strengths of 32.5% and 40% were investigated further in two dose-ranging studies (A-101-SEBK-202 and A-101-SEBK-203). A-101-SEBK-202 evaluated the effectiveness of the two strengths for the treatment of SK lesions on the trunk and extremities; A-101-SEBK-203 evaluated the effectiveness of the two strengths for the treatment of SK lesions on the face. Both studies demonstrated that the strength of 40% was superior to vehicle and to the strength of 32.5% for safely and effectively treating SK lesions in adult subjects (**Tables 2.2.2.1 and 2.2.2.2**) and had an acceptable safety profile (data not shown).

2.2.3 Have the Phase 3 pivotal trials demonstrated evidence of effectiveness?

Yes. The overall Phase 3 efficacy results have demonstrated that ESKATA is effective for the treatment of raised SK lesions in adult patients.

Both pivotal studies A-101-SEBK-301 and A-101-SEBK-302 demonstrated statistically significant treatment effect of ESKATA compared to vehicle control (**Table 2.2.3.1**). In the Phase 3 studies, subjects received a study medication treatment on four eligible SK target lesions, including at least one on the face and at least one on the trunk or extremities at Visit 2 (Day 1). The primary efficacy variable was the Physician's lesion assessment (PLA) and the primary endpoint was target lesions that were judged to be clear on the PLA (PLA = 0) at Visit 8 (Day 106).

At Visit 4 (Day 22), any target lesion that had a PLA grade of > 0, received a second study medication treatment unless either of the following criteria applied:

- The target lesion had a Visit 4 pre-treatment local skin reaction (LSR) grade of 3 (severe) for any sign or symptom and the grade had increased compared to the Visit 3 grade.
- The target lesion was, in the investigator's opinion, not appropriate for a retreatment.

Table 2.2.2.1. Study A-101-SEBK-202: PLA average percent of target lesions (on the trunk and extremities) clear (PLA = 0) by visit and treatment.

Visit Statistic	Vehicle (N = 57)	A-101 Solution 32.5% (n = 56)	A-101 Solution 40% (N = 56)
Baseline (Visit 2), N	57	56	56
Mean (SD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Range	0 to 0	0 to 0	0 to 0
Visit 4 (Day 22), N	57	56	56
Mean (SD)	0.88 (6.62)	13.39 (28.59)	20.98 (36.24)
Range	0 to 50	0 to 100	0 to 100
p-value[a]	NA	0.0142	0.0001
p-value[b]	NA	0.1366	
Visit 6 (Day 50), N	57	55	55
Mean (SD)	4.82 (17.95)	18.64 (28.95)	32.27 (34.59)
Range	0 to 100	0 to 100	0 to 100
p-value[a]	NA	0.0097	< 0.0001
p-value[b]	NA	0.0114	
Visit 7 (Day 78), N	57	56	56
Mean (SD)	4.82 (17.95)	24.11 (34.03)	39.73 (35.60)
Range	0 to 100	0 to 100	0 to 100
p-value[a]	NA	0.0009	< 0.0001
p-value[b]	NA	0.0069	
Visit 8 (Day 106), N	57	56	56
Mean (SD)	4.82 (15.26)	26.79 (38.10)	45.09 (37.06)
Range	0 to 75	0 to 100	0 to 100
p-value[a]	NA	0.0003	< 0.0001
p-value[b]	NA	0.0027	

Note: The SK target lesions were on the trunk and extremities.

a P-value comparing vehicle versus other treatment group using ANOVA model

b P-value comparing A-101 solution 32.5 % against A-101 solution 40 % treatment groups using ANOVA model

Source: A-101-SEBK-202 CSR, Section 14.2, Table 9.3.1 and Table 9.3.1A

Table 2.2.2.2. Study A-101-SEBK-203: number and percentage of PLA responders with target lesion (on the face) clear (PLA = 0) by visit and treatment.

Visit Statistic	Vehicle (N = 41)	A-101 Solution 32.5% (n = 39)	A-101 Solution 40% (N = 39)
Visit 4 (Day 22), N	40	39	37
N (%)	0 (0.0%)	11 (28.21%)	9 (24.32)
p-value[a]	NA	0.0003	0.0009
Visit 6 (Day 50), N	40	39	37
N (%)	2 (5.0%)	18 (46.15%)	24 (64.86%)
p-value[a]	NA	< 0.0001	< 0.0001
Visit 7 (Day 78), N	40	39	37
N (%)	1 (2.50%)	19 (48.72%)	22 (59.46%)
p-value[a]	NA	< 0.0001	< 0.0001
Visit 8 (Day 106), N	40	39	37
N (%)	1 (2.50%)	18 (46.15%)	22 (59.46%)
p-value[a]	NA	< 0.0001	< 0.0001

Note: The SK target lesion was on the face.

a P-value comparing vehicle versus other treatment group using chi-square test

Source: A-101-SEBK-203 CSR, Section 14.2, Table 9.3.1

Table 2.2.3.1. Primary efficacy results of Phase 3 Studies A-101-SEBK-301 and A-101-SEBK-302.
[a]The Cochran-Mantel-Haenszel (CMH) test stratified by center tests the null hypothesis that the difference in proportion of responders between the two treatment groups = 0, 2-tail alpha=0.05. *(Source of data: Table 10, Summary of Clinical Efficacy*)

Analysis on Day 106	Study A-101-SEBK-301			Study A-101-SEBK-302		
	ESKATA (N = 223)	Vehicle Solution (N = 227)	P-value	ESKATA (N = 244)	Vehicle Solution (N = 243)	P-value
All 4 lesions clear (primary efficacy analysis)	4.04%	0%	0.0019 [a]	7.79%	0%	<0.0001[a]

2.2.4 What is the pharmacokinetics (PK) of hydrogen peroxide under maximal use conditions?

Measurement of hydrogen peroxide concentrations in systemic circulation was not conducted in the development program following application of ESKATA in patients with SK lesions; however, the applicant measured changes in concentration ratio of GSH/GSSG in blood following a single treatment of ESKATA to ten SK lesions (with at least one lesion on the face) in patients. The GSH/GSSG ratio in post-treatment blood samples did not change significantly following application of ESKATA when compared to that in pre-dose samples (**Figure 1.3.1**), suggesting no systemic absorption of hydrogen peroxide resulting from the topical application of ESKATA. See additional details in **Section 1.3** and **Appendix** of this review.

2.2.5 What information is submitted to assess or waive TQT trial?

The Applicant submitted a waiver of thorough QT/QTc (TQT) study for ESKATA on 5/16/2017. The QT Interdisciplinary Review Team reviewed the waiver request and agreed to a waiver for a thorough QT/QTc study (*refer to the review by Dr. Marathe dated 8/31/2017 in DARRTS*).

2.3 Intrinsic Factors

2.3.1 Pediatric subjects

The Applicant requested a full waiver of the requirement to conduct studies in pediatric patients from 0 to 17 years of age. The Agency has agreed to the Applicant's request.

2.4 Extrinsic Factors

2.4.1 Drug-drug interactions

Drug-drug interactions were not evaluated for ESKATA. This is acceptable because the product will be applied during a single in-office treatment session and the maximal use study results suggested no systemic absorption of hydrogen peroxide following application of ESKATA.

2.5 Bioanalytical Methods

The bioanalytical method for measurement of GSH and GSSG in blood was validated. However, details are not included in this review because systemic absorption of hydrogen peroxide following administration of ESKATA is not expected to occur due to the decomposition into water and reactive oxygen species upon topical application.

3 Detailed Labeling Recommendations

The following changes are recommended for sections 12 of the label for ESKATA Solution, 40%. Deletions are noted as ~~strikethrough~~ and additions are noted as double underlines.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action for ESKATA for the treatment of raised seborrheic keratoses is unknown (b) (4)

(b) (4)

12.2 Pharmacodynamics

The pharmacodynamics of ESKATA in the treatment of raised seborrheic keratoses are unknown.

12.3 Pharmacokinetics

(b) (4)

(b) (4) Following application of ESKATA in patients with seborrheic keratosis lesions, hydrogen peroxide rapidly dissociates into water and reactive oxygen species. Indirect assessment of reactive oxygen species in

patients with seborrheic keratosis lesions did not demonstrate any systemic absorption of hydrogen peroxide.

4 Appendix: Individual Study Summary

4.1 Study A-101-SEBK-205

Reviewer's note: *ESKATA was referred to as A-101 (hydrogen peroxide) Solution 40% during development.*

Title: A Within Subject Study of the Bioavailability of A-101 Topical Solution Administered Under Maximum Use Conditions in Subjects with Seborrheic Keratosis

Studied period:

Study Initiation Date (First Patient Enrolled): 09 May 2016
Study Completion Date (Last Patient Completed): 27 July 2016

Objectives:

The main objective of this study was to assess whether treatment with the to-be-marketed A-101 (hydrogen peroxide) Solution 40% under maximum use conditions would lead to an increase over endogenous levels of hydrogen peroxide in the blood of subjects with seborrheic keratosis (SK) on the trunk, extremities, and face. A further objective of this study was to evaluate the safety of A-101 Solution 40% administered topically under conditions of maximum use in subjects with SK on the trunk, extremities, and face.

Study design:

Twenty-four subjects (12 females and 12 males) were enrolled in the study. Each subject had 10 eligible SK target lesions (see more details in **Diagnosis and main criteria for inclusion**) on the trunk, extremities, and face (including at least 1 target lesion on the face). Each SK target lesion was treated once with A-101 Solution 40% at Visit 3.

There were 5 study visits:

- At Visit 1, the investigator identified the eligible SK target lesions and the eligibility assessment period began.
- At Visit 2 (within 14 days after Visit 1), the investigator collected blood samples for analyzing baseline level of reduced glutathione (GSH) and glutathione disulfide (GSSG).
- At Visit 3 (Day 1, within 7 days of Visit 2), the investigator performed an A-101 Solution 40% study medication treatment to the target lesions and collected blood samples.
- At Visit 4 (Day 8), subjects were seen for a no-treatment follow-up.
- At Visit 5 (Day 29), subjects were seen for a no-treatment follow-up and were discharged from the study.

The duration of study participation was a maximum of 53 days per subject.

Assessment of GSH and GSSG concentrations and their ratio in blood:

Blood samples were collected at pre-dose, 15 min, 30 min, and 1, 2, 4, 6 hours after treatment during Visit 3 (treatment applied) and at matched time points during Visit 2 (baseline, no treatment). GSH and GSSG concentrations in blood were measured using a validated high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS). The ratios of GSH to GSSG were calculated.

Diagnosis and main criteria for inclusion: Subjects were at least 18 years of age with a clinical diagnosis of stable clinically typical SK and 10 appropriate SK target lesions on the trunk, extremities, and face (including at least 1 target lesion on the face). Each target lesion had a clinically typical appearance; length ≥ 5 mm and ≤ 15 mm and width ≥ 5 mm and ≤ 15 mm on the trunk and extremities; length ≥ 3 mm and ≤ 15 mm and width ≥ 3 mm and ≤ 15 mm on the face; was a discrete lesion surrounded with sufficient non-lesional skin so that (in the investigator's opinion) no other SK lesion would have interfered with study medication treatment or study evaluations; was not covered with hair that (in the investigator's opinion) would have interfered with the study medication treatment or the study evaluations, was not in an intertriginous fold, was not pedunculated, was not on the eyelids, and was not within 5 mm of the orbital rim. Female subjects were nonpregnant and nonlactating, and women of childbearing potential had a negative urine pregnancy test and agreed to use an approved effective form of birth control for the duration of the study. Subjects were in good general health and free of any disease state or physical condition that, in the investigator's opinion, might have interfered with study evaluations or that exposed the subject to an unacceptable risk by study participation.

Number of subjects (planned and analyzed):
Approximately 24 subjects were planned. A total of 24 were enrolled, treated, and analyzed.

Test product, dose and mode of administration, batch number:
A-101 Solution 40% (Lot 1035A15) was applied topically to target lesions by an investigational center staff member.

Treatment duration:
A single study medication treatment took place at Visit 3 for all target lesions.

Criteria for evaluation:
Measures for systemic hydrogen peroxide exposure: Due to the reactivity and lability of H_2O_2 and difficulties of making direct measurements of blood or plasma H_2O_2 levels, an indirect assessment was made of changes in blood exposure to H_2O_2 by measuring GSH and GSSG levels in whole blood and calculating the GSH/GSSG ratio.

Safety measures: Treatment-emergent adverse events, local skin reactions, clinical laboratory evaluations (chemistry, hematology), and vital signs.

Results:
Reviewer note*: This section focuses only on the results of GSH/GSSG. For safety and efficacy results, please see clinical review.*

Demographics:
Twenty-four adult subjects (12 males and 12 females) were enrolled and all enrolled subjects completed the study. The mean age was 70.9 years (range 57 to 87 years) and all subjects were white.

Changes in blood levels of GSH/GSSG following A-101 (hydrogen peroxide) Solution 40% treatment:

Blood concentrations of GSH and GSSG were measured and GSH/GSSG ratios were calculated for each subject from pre-dose to 6 hours post-dose at Visit 3 (A-101 applied) and at matched time points of Visit 2 (no treatment). Percentage of change in GSH/GSSG of blood samples was calculated relative to the GSH/GSSG value of the first sample (baseline) collected at each visit. At Visit 2 (no treatment), no significant change in GSH/GSSG was observed compared to the first sample during the 6-hour period and the maximum mean % change in GSH/GSSG ratio was -3%. During Visit 3 (A-101 applied), there was an overall increase in the GSH/GSSG ratio following the treatment using A-101 (hydrogen peroxide) Solution 40% and the maximum mean % change in GSH/GSSG ratio relative to pre-dose was 8% (**Figure 1.3.1**). These changes were not significantly different from 0 (no change). Therefore, GSH/GSSG did not decrease following the topical application of A-101 (hydrogen peroxide) Solution 40%. This indicated that there was no increase in blood exposure to H_2O_2 caused by the topical application of A-101.

Reviewer's comments*: Hydrogen peroxide is a member of the class of reactive oxygen species (ROS) which are generated via respiratory chain cascade and as byproducts of cellular metabolism in biological systems. Various detoxifying enzymes expressed in humans such as glutathione peroxidases, catalases, and peroxiredoxins can rapidly degrade hydrogen peroxide to maintain the cellular redox homeostasis [Lennicke et al. Cell Communication and Signaling (2015) 13:39]. The biological system of humans has several defense systems against oxidative stress. The glutathione system is a major thiol-based defense system against oxidative stress in mammals and functions as co-substrate for the glutathione peroxidases, which efficiently remove hydrogen peroxide. Hydrogen peroxide also reacts with the thiol (-SH) group on free cysteine or protein, ascorbic acid, and other antioxidants. Because of the reactivity of hydrogen peroxide, measuring systemic exposure of hydrogen peroxide is challenging.*

To satisfy the bioavailability requirement for this NDA, the applicant conducted this study to indirectly evaluate systemic exposure of hydrogen peroxide resulting from ESKATA by evaluating the ratio of glutathione reduced form (GSH) to glutathione disulfide (GSSG) in blood because GSH can be converted to GSSG in the presence of oxidative stress that includes hydrogen peroxide. The applicant did not observe a significant change in the ratio of GSH/GSSG in blood following the topical application of ESKATA under maximal use conditions compared to pre-dose value, indicating that hydrogen peroxide from ESKATA was not absorbed in blood. From a Clinical Pharmacology's perspective, information submitted by the applicant to address the bioavailability requirement of the NDA is acceptable.

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/s/

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