CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209305Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209305
Priority or Standard	Standard
Submit Date(s)	February 24, 2017
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Division / Office	DDDP/ODEIII/OND/CDER
Reviewer Name(s)	Melissa Reyes
Review Completion Date	November 21, 2017
Established Name	hydrogen peroxide
(Proposed) Trade Name	Eskata
Applicant	Aclaris Therapeutics, Inc.
Formulation(s)	Solution, 40% for topical application
Dosing Regimen	Once every minute for 4 applications in one treatment up to (b)(4) treatments.
Indication(s)	Treatment of seborrheic keratosis that are raised.
Intended Population(s)	18 years of age and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that hydrogen peroxide solution, 40% for topical application be approved for the treatment seborrheic keratoses that are raised.

1.2 Risk Benefit Assessment

In this NDA, the applicant requests approval for their product, hydrogen peroxide (HP) solution, 40% for topical application for the treatment of seborrheic keratosis. In support of this indication, the applicant conducted two well-controlled Phase 3 trials.

The primary evidence of efficacy was based on two well-controlled trials of similar design, A-101-SEBK-301 (SEBK-301) and A-101-SEBK-302 (SEBK-302). These two Phase 3 trials were randomized, multicenter, double-blind, placebo-controlled, 15-week trials that evaluated the safety and efficacy of HP solution, 40% for topical application for the treatment of SKs that are raised on the face, trunk and extremities in adult subjects. The two trials randomized 937 subjects, 18 years and older, who had four seborrheic keratosis target lesions (SKTLs) with at least one seborrheic keratosis target lesion (SKTL) on the face and with at least one SKTL on the trunk or extremities. Subjects received investigator-applied treatment on Day 1 with a second treatment if the SKTL was still present, at Day 22. Treatment consisted of topical application of HP solution, 40% to the SKTL, waiting one minute, and then re-applying for a total of four applications per lesion, per treatment session.

The primary endpoint was the proportion of subjects with clearance of all SKTLs (PLA = 0) at Visit 8/Day 106. In the trial SEBK-301, 4% of HP solution, 40% treated subjects and 0% of vehicle treated subjects achieved clearance of all four SKTLs, a treatment effect of 4% ($p < 0.001$). In the trial SEBK-302, 8% of HP solution, 40% treated subjects and 0% of vehicle treated subjects achieved clearance of all four SKTLs, a treatment effect of 8% ($p < 0.001$).

A major secondary endpoint was the proportion of subjects who achieved clearance of three or more SKTLs at Day 106 compared to baseline. In the trial SEBK-301, 13% of HP solution, 40% treated subjects and 0% of vehicle treated subjects achieved clearance of three or more STKLs ($p < 0.001$) while in the trial SEBK-302, 23% of HP solution, 40% treated subjects and 0% of vehicle treated subjects achieved clearance of three or more SKTLs ($p < 0.001$).

The data from these two Phase 3 trials provided evidence of efficacy for HP solution, 40% in the target population.

Efficacy, although modest, was consistent across sub-groups (by age, gender, race, ethnicity). Evaluation of consistency across study centers revealed that, in trial SEBK-302, nearly half of responders were from one site. Exclusion of this high responder site in the efficacy analyses, still led to clinical significance of the primary and secondary efficacy endpoints. The clearance rate of SKTLs on the face was higher than the clearance rate of SKTLs on the trunk or extremities. Smaller and thinner SKTLs were slightly more likely to achieve clearance than lesions that were larger or thicker.

The assessment of safety for the HP solution, 40% was primarily based on analysis of data from two Phase 3 trials (SEBK-301 and SEBK-302). The safety population included 467 subjects exposed to at least one treatment of HP solution, 40% with 98% subjects receiving re-treatment of at least one SKTL on Day 22.

During the development program for HP solution, 40%, one death (metastatic malignancy) was reported in HP 40% treated subject. Detailed analysis of this event did not suggest a causal relationship.

In the Phase 3 trials (SEBK-301 and SEBK-302), 10 subjects who were treated with HP solution, 40% experienced 14 SAEs and 10 subjects who were treated with vehicle experienced 11 SAEs. No SAE was related to study drug.

In Phase 2 trials and open-label Phase 3 Trial (SEBK-303), 6 subjects who were treated with HP solution, 40% experienced 6 SAEs and 2 subjects who were treated with vehicle experienced 2 SAEs. No SAE across these trials was related to study drug.

The most frequently reported adverse reactions were local skin reactions (LSR): pruritus, stinging, erythema, crusting, edema and scaling.

In this reviewer's opinion, the applicant provided adequate evidence of safety of HP solution, 40%.

This reviewer concludes that HP solution, 40% for topical application has acceptable risk/benefit profile for the treatment of subjects with SKs that are raised on the face, trunk and extremities. An approval action for this NDA is recommended, pending final labeling negotiations with the applicant.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements and commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

The applicant's product is a hydrogen peroxide solution of 40% with the proposed trade name Eskata. Hydrogen peroxide is an oxidizing agent that is a colorless, odor-less liquid.

The applicant's proposed indication is for the treatment SK lesions on the face, trunk and extremities in adults. Eskata will be packaged within a glass ampoule surrounded by a cardboard applicator. This will allow crushing of the glass ampoule to allow drug to be filtered prior to application on the skin via an applicator tip at one end of the applicator.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no currently approved treatments for the treatment of SK.

2.3 Availability of Proposed Active Ingredient in the United States

As a 3% solution, HP is currently marketed in the United under monograph for the following indications:

- external analgesic, poison ivy
- oral healthcare, wound cleansing panel
- oral health care
- antimicrobial
- gingivitis/plaque

2.4 Important Safety Issues with Consideration to Related Drugs

HP is an oxidizing and corrosive agent and therefore a potential skin and ocular irritant. In general, risks associated with skin and mucosal irritants are: erythema, edema, vesiculation, erosion, ulceration, scaling, crusting, scaring, hyperpigmentation, and hypopigmentation. Eye exposure to HP may result in erosion, ulceration, corneal perforation, scaring, chemical conjunctivitis, eyelid edema and severe pain.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development program for the SK indication was conducted under IND 117635 which was opened on September 16, 2013. Key pre-submission regulatory activities include the following:

- End-of-Phase 2 meeting (May 6, 2015)
- Pre-NDA meeting (September 28, 2016)

End-of-Phase 2 meeting was held on May 6, 2015.
The following advice was conveyed to the sponsor:

- The Agency advised submitting information and a sample of the delivery device prior to initiation of Phase 3 trials. A different device was used in Phase 2 trials.
- The applicant agreed to the Agency's advice to enroll subjects with at least four SK lesions on the trunk, extremities and face and success defined as complete clearance of all four SKTLs as the primary endpoint.
- Sponsor clarified intent to limit distribution to in office practice based on need for diagnosis of SK lesions by a practitioner.

Pre-NDA meeting was held on September 28, 2016.
The content and format of the proposed NDA submission was discussed.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Office of Scientific Investigations (OSI) inspections were requested for four Phase 3 study sites, selected because they had some of the highest enrollment numbers, high site efficacy effect and no prior history of Good Clinical Practice (GCP) inspection.

Study A-101-SEBK-301 (SEBK-301)

- Investigator: Stacy Smith, Study site #14; enrolled 23 subjects

Study A-101-SEBK-302 (SEBK-302)

- Investigator: Andrew Pollack, Study site #14; enrolled 43 subjects

Investigation of Study SEBK-301 Site 14 identified one subject with inclusion criteria violation (SKTL larger than upper limit of 15 mm length) that was enrolled in the HP solution, 40% arm. The OSI review classified the site violation as VAI (voluntary action indicated) as the data obtained from the subject may impact the efficacy signal of the

study drug. As any impact on the efficacy effect due to larger lesion size would likely decrease the efficacy effect, the data from Dr. Smith's site was deemed acceptable for inclusion in the analysis.

Investigation of Study SEBK-302 Site 14 resulted in a site classification of NAI (no action indicated).

3.2 Compliance with Good Clinical Practices

The applicant stated that studies were designed, monitored, and conducted in accordance with Good Clinical Practice requirements and ethical principles. Trial protocols, the subject information and informed consent forms, subject recruitment procedures were reviewed by the responsible Institutional Review Board (IRB). The applicant obtained an approval from the IRB prior to trial initiation.

3.3 Financial Disclosures

The sponsor certified (Form 3454) that they had not entered into financial arrangements with any of the clinical investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry, Manufacturing, and Control (CMC) reviewer recommends approval of hydrogen peroxide 40% solution. The applicant provided sufficient information to assure identity, strength, purity and quality of the drug product.

Hydrogen peroxide (HP) is a colorless, odorless liquid that is a known irritant as an oxidizing agent. It is extremely labile and rapidly degrades to water and oxygen.

Table 1: Composition of A-101 (Hydrogen Peroxide) 40% Topical Solution

Steril USP	(b) (4) (b) (4) (b) (4)	(b) (4)

Source: Agency CMC Review

The applicant's proposed container applicator encloses HP solution, 40% in a glass ampoule. The ampoule is crushed prior to application releasing the HP solution, 40%

which is filtered prior to reaching an applicator tip used to wet the SK lesion. The flocked tip is used to apply HP solution, 40% to the SKTL.

Figure 1: Container Applicator for HP solution, 40%

(b) (4)

To prevent dispensing glass particles created by crushing the ampoule, the applicator contains a filter between the ampoule and the flocked applicator tip. The filter removes glass particles prior to HP solution, 40% application to the SKTL. To assure quality of the product, the applicant evaluated glass particles dispensed by the applicator. During the development (b) (4) The CMC reviewer deemed the change "satisfactory."

For more information, refer to the review of the CMC review team and Integrated Quality Assessment by Yichun Sun, PhD.

4.2 Clinical Microbiology

This section of the review is not applicable to this product.

4.3 Preclinical Pharmacology/Toxicology

Topical application in rats and minipigs did not show any systemic toxicity, and no penetration occurred through dermatomed minipig and human skin (Franz pump). Thus, safety pharmacology studies were not conducted.

Carcinogenicity studies were deemed not warranted due to" the short duration of treatment, lack of dermal absorption and systemic toxicity, and negative non-mutagenic and non-clastogenic behavior observed in *in vivo* genotoxicity studies." For these same reasons, reproductive and developmental studies are not warranted for HP solution, 40%.

Reviewer's comment: The Agency's Cancer Assessment Committee (CAC) has reviewed the carcinogenicity risk of HP in tooth whitening products. Based on in vivo *genotoxicity assays and long-term bioassays, CAC concluded HP is not a carcinogen and that tumor production will not occur in humans as a result of HP exposure.*

Pharmacology/Toxicology reviewer, Dr. Kumar Mainigi, is recommending an approval of this NDA. No postmarketing requirement was recommended by Dr. Mainigi.

The reader is referred to the Pharmacology/Toxicology reviews by Kumar Mainigi, PhD, and Barbara Hill, PhD for detailed analysis of the non-clinical pharmacology and toxicology aspects of this application.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action for ESKATA for the treatment of SK is unknown.

4.4.2 Pharmacodynamics

The applicant did not conduct pharmacodynamic studies as part of the HP solution, 40% development program. The pharmacodynamics of ESKATA in the treatment of SK are unknown.

4.4.3 Pharmacokinetics

The applicant conducted an open label pharmacokinetic study A-101-SEBK-205 in 24 subjects. HP solution, 40% was applied topically to a total of 10 SKTLs located on the face (at least 1 SKTL), trunk and extremities for each subject to assess systemic exposure. Baseline blood levels were measured up to seven days prior to treatment and compared to blood levels drawn on the day of treatment. As HP rapidly degrades, direct measurement of HP was not possible. Reduced glutathione (GSH) can be converted to glutathione disulfide (GSSG) in the presence of oxidative stress such as HP. Change in the GSH/GSSG ratio after treatment was used to evaluate systemic exposure to HP. There was no decrease in the GSH/GSSG ratio in the samples collected over 6-hours post-treatment compared to pre-treatment values at the same time points. The study determined no detectable increase in systemic HP levels following HP 40% application.

The applicant also evaluated clinical safety of the HP solution, 40% treatment by assessing local skin reactions, AEs, laboratory testing (comprehensive chemistry and hematology panels) and vital signs. No deaths, SAEs or drug-related AEs occurred. Local skin reactions were predominantly mild.

The reader is referred to the Clinical Pharmacology review by Yanhui Liu, PhD, for detailed analysis of the clinical pharmacology aspects of this application.

5 Sources of Clinical Data

The applicant conducted five clinical trials in the development program for SK.

5.1 Tables of Studies/Clinical Trials

Table 2: Trials Supporting the Application

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
Phase 3 Pivotal Trials						
SEBK-301 Pivotal – Safety and Efficacy Completed	Phase 3, multicenter (MC), randomized (R), double-blind (DB), vehicle-controlled (VC), parallel group trial	HP solution, 40% topically on Day (D) 1, could be retreated on D22	Clearance of all four treated SK target lesions	End of study visit on D106	450 – R 227 – vehicle 223 – HP 40%	SK on trunk, extremities, and face with at least 1 target lesion on the face and at least 1 target lesion on the trunk or extremities. Target lesions have clinically typical appearance, PLA of ≥ 2, length ≥ 5 mm and ≤ 15 mm, width ≥ 5 mm and ≤ 15 mm, thickness ≤ 2 mm, and are discrete lesions
SEBK-302 Pivotal – Safety and Efficacy Completed	Same as SEBK-301	Same as SEBK-301	Same as SEBK-301	Same as SEBK-301	487 – R 243 – vehicle 244 – HP 40%	Same as SEBK-301

Phase 1/2/3						
SEBK-201 Completed	Phase 2, R, DB, VC, within-subject comparison trial	HP 32.5%, 40% or vehicle topically on D1, could be retreated on D22	Efficacy and safety of HP 25%, 32.5%, and 40% compared to vehicle	End of study visit on D78	35 subjects - SK lesions randomized to HP 25%, 32.5%, and 40%, and vehicle	Adults with at least 4 appropriate SK target lesions on the back
SEBK-202 Completed	Phase 2, MC, R, DB, VC, parallel-group study	HP 32.5%, 40% or vehicle topically on D1, could be retreated on D22	To evaluate dose-response, safety, and efficacy HP 32.5% and 40% compared to vehicle	End of study visit on D106	172 – R 57 – HP 40% 57 – HP 32.5% 58 – vehicle	At least 18 years of age with a clinical diagnosis of stable clinically typical SK with at least 4 appropriate SK target lesions on the trunk/ extremities
SEBK-203 Completed	Phase 2, MC, R, DB, VC, parallel-group study	HP 32.5%, 40% or vehicle solution topically applied on D2, could be retreated on D22	To evaluate dose-response relationship, safety, and efficacy of 40% compared to vehicle	End of study visit on D106	119 – R 39 – HP 40% 39 – HP 32.5% 41 – vehicle	Adults with Fitzpatrick skin type of 1 to 4, a clinical diagnosis of stable clinically typical SK, and 1 appropriate SK target lesion on the face with clinically typical appearance, treatment naïve, PLA of ≥ 2, length ≥ 7 mm and ≤ 15 mm, width ≥ 7 mm and ≤ 15 mm, thickness ≤ 2 mm, discrete lesion
SEBK-205 Completed	Phase 2, open-label, within subject study	HP 40% single topical application to 10 SK lesions, including one lesion on the face	Safety	29 days	24 – A101	Adults with clinical diagnosis of stable clinically typical SK and 10 appropriate SK target lesions on trunk, extremities, and face (including at least 1 target lesion on the face)

RIPT-101 Completed	Phase 1, within-subject study with HP 40%, vehicle, and controls of sodium lauryl sulfate and white petrolatum	HP 40% topically 3 times/week for 3 weeks, 2-week rest, single challenge application	Sensitization potential of HP 40%	39 days	233 – HP 40%	Healthy adults
SEBK-303 Completed	Phase 3, MC, open-label	HP solution, 40% topical to lesion(s) on D1, could be retreated on D22, D43, and D64	To evaluate the safety of HP 40% after treatment of 4 SK target lesions on the trunk, extremities and face, and the clinical effects based on PLA scores evaluated at each post-baseline visit	End of study visit D148	147 – HP 40%	Adults with 4 SK on trunk, extremities, and face. Target lesions have clinically typical appearance, length ≥ 5 mm and ≤ 15 mm, width ≥ 5 mm, and ≤ 15 mm, thickness ≤ 2 mm
HS 06429-02 Completed	Single center, DB, PC	35% stock solution of HP topically applied up to 6 times over 3 months to epidermal proliferations, including SK	Total number of remaining SKs in all patients at D90 after up to 6 treatments compared to D0	3 months	32	Individuals with benign epidermal proliferations, including SK

PLA: Physician Lesion Assessment score
Source: Modified from applicant's submission, Module 5.3.5.3 ISE, Table 1, page 6

5.2 Review Strategy

For safety, trials SEBK-301 and SEBK-302 were reviewed as pooled data and discussed in section 7 of this review. Data from other trials in this development program for this indication were used as supporting evidence. Raw datasets were reviewed in conjunction with the applicant's clinical study reports (CSRs) and Integrated Summary of Safety (ISS).

For efficacy, two Phase 3 trials, SEBK-301 and SEBK-302, will be reviewed separately and pooled, and discussed in section 6 of this review.

5.3 Discussion of Individual Studies/Clinical Trials

Two Phase 3 trials (SEBK-301 and SEBK-302) and four Phase 2 trials (SEBK-201, SEBK-202, SEBK-203 and SEBK-205) support this NDA. The applicant also conducted a dermal safety study, A-101-RIPT-101 (RIPT-101), and an open-label Phase 3 study, A-101-SEBK-303, as part of the development program.

Phase 3 Trial: A-101-SEBK-301 (SEBK-301)

Study Title: A randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of hydrogen peroxide (A-101) solution 40% in subjects with seborrheic keratosis (SK) on the trunk, extremities and face (study 1)

Study Period: February 3, 2016 – November 4, 2016

Study Objective: to evaluate the effectiveness of the to-be-marketed formulation hydrogen peroxide (HP) solution 40% when applied to four seborrheic keratosis target lesions (SKTLs) on the trunk, extremities and face compared with a matching solution vehicle

Study Design: This was a randomized, double-blind, vehicle-controlled, parallel group, multi-center study.

Number of Centers: 17 in the United States

Number of Subjects: 450 subjects were randomized

Study Population
Key Inclusion Criteria:

1. Subject is at least 18 years of age
2. Subject has a clinical diagnosis of stable clinically typical seborrheic keratosis
3. Subject has four appropriate SKTLs on the trunk, extremities and face, with at least one target lesion on the face and at least one target lesion on the trunk or extremities, that each are eligible for treatment as defined below:
    a) Have a clinically typical appearance
    b) Have a Physician Lesion Assessment of ≥2
    c) Have a length that is ≥5mm and ≤15mm
    d) Have a width that is ≥5mm and ≤1 5mm
    e) Have a thickness that is ≤2mm
    f) Be a discrete lesion
    g) Be, when centered in the area outlined by the provided circular template, the only SK lesion present
    h) Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
    i) Not be in an intertriginous fold
    j) Not be on the eyelids
    k) Not be within 5mm of the orbital rim
    l) Not be pedunculated.
4. If the subject is a woman of childbearing potential, she has a negative urine pregnancy test and agrees to use an active method of birth control for the duration of the study
5. Subject is non-pregnant and non-lactating

6. Subject is in good general health and free of any known disease state or physical condition which, in the investigator's opinion, might impair evaluation of any target lesion or which exposes the subject to an unacceptable risk by study participation
7. Subject is willing and able to follow all study instructions and to attend all study visits
8. Subject is able to comprehend and willing to sign an informed consent form.

Physician Lesion Assessment (PLA)
The PLA is an investigator assessment of SK lesion severity based on presence of SK and thickness of SK. The PLA was determined for all subjects for each SK target lesion (SKTL) at Visit 1/screening, Visit 2 pre-treatment/Baseline, Visit 4 pre-treatment, Visit 6, Visit 7 and Visit 8.

Table 3: Physician Lesion Assessment Scale

Physician's Lesion Assessment	
Grade	Descriptor
0	Clear: no visible seborrheic keratosis lesion
1	Near Clear: a visible seborrheic keratosis lesion with a surface appearance different from the surrounding skin (not elevated)
2	Thin: a visible seborrheic keratosis lesion (thickness ≤1mm)
3	Thick: a visible seborrheic keratosis lesion (thickness >1mm)

Source: Applicant's submission; Protocol; A-101-SEBK-301; Section 6.1.1; PLA, page 41.

Key Exclusion Criteria:

1. Subject has clinically atypical and/or rapidly growing seborrheic keratosis lesions
2. Subject has presence of multiple eruptive SK lesions (Sign of Lesser-Trelat)
3. Subject has a current systemic malignancy
4. Subject has used any of the following systemic therapies within the specified period prior to Visit 1:
    a. Retinoids; 180 days
    b. Glucocorticosteroids; 28 days
    c. Anti-metabolites (e.g., methotrexate); 28 days
5. Subject has used any of the following topical therapies within the specified period prior to Visit 1 on, or in a proximity to any target lesion, that in the investigator's opinion interferes with the study medication treatment or the study assessments:
    a. LASER, light or other energy based therapy (e.g., intense pulsed light [IPL], photo-dynamic therapy [PDT]); 180 days
    b. Liquid nitrogen, electrodesiccation, curettage, imiquimod, 5-flurouracil, or ingenol mebutate; 60 days
    c. Retinoids; 28 days
    d. Microdermabrasion or superficial chemical peels: 14 days
    e. Glucocorticosteroids or antibiotics; 14 days

6. Subject currently has or has had any of the following within the specified period prior to Visit 1 on or in a proximity to any target lesion that, in the investigator's opinion, interferes with the study medication treatment or the study assessments:
    a. A cutaneous malignancy; 180 days
    b. A sunburn; currently
    c. A pre-malignancy (e.g., actinic keratosis); currently
    d. Body art (e.g., tattoos, piercing, etc.); currently
    e. Excessive tan; currently
7. Subject has a history of sensitivity to any of the ingredients in the study medications
8. Subject has any current skin disease (e.g., psoriasis, atopic dermatitis, eczema, sun damage, etc.), or condition (e.g., sunburn, excessive hair, open wounds) that, in the opinion of the investigator, might put the subject at undue risk by study participation or interfere with the study conduct or evaluations
9. Subject has participated in an investigational drug trial in which administration of an investigational study medication occurred within 30 days prior to Visit 1.

Study Visits and Procedures

This trial consisted of treatment with study drug on Visit 2/Day 1 of four STKLs (all with PLA $\geq$ 2) and re-treatment on Visit 4/Day 22, if the SKTL had a PLA $\geq$ 0. Active monitoring was done for hair discoloration and local skin reactions (LSR). LSR included subject assessments for pruritus and stinging and investigator assessments for erythema, edema, scaling/dryness, vesicles/bullae, crusting, erosion, ulceration, postinflammatory hypopigmentation, postinflammatory hyperpigmentation, atrophy and scarring.

Table 4: Trial SEBK-301 Study Flow Chart

Visit	1	2	3	4	5	6	7	8
Day	-13 to 0	1	8	22	29	50	78	106
Informed consent	X							
Subject identifier	X							
Inclusion/exclusion criteria	X							
Demographics & medical history	X							
Vital signs	X	X[1]						X
Clinical laboratory sampling	X							X
Urine pregnancy tests	X	X[1]						X
Target Lesion identification	X							
Physician's lesion assessment	X	X[1]		X[1]		X	X	X
Lesion dimensions	X	X[1]						
Local skin reactions		X[2]	X	X[2]	X	X	X	X
Standardized photography	X	X[1]						X
Subject randomization		X[1]						
Study medication treatment		X		X[3]				
Subject instructions	X	X	X	X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X

[1] Performed prior to the study medication treatment
[2] Performed prior to and after completion of the study medication treatment
[3] Only for Target Lesions that meet the retreatment criteria.

Source: Applicant's submission; Protocol; A-101-SEBK-301; Section 5.2; Study Flow Chart, page 20.

Investigational Product

Investigational product (IP) was to be applied by the investigator in the clinic setting on Day 1. If an SKTL had a PLA $\geq$ 0 on Day 22, the lesion was re-treated unless the SKTL:

- had a pre-treatment LSR grade of 3 for any sign or symptoms AND the grade increased compared to the previous visit
- was considered not appropriate for re-treatment by the investigator

Treatment included 4 applications of IP to the lesion separated by 1 minute drying time.

Concomitant Medication

Previous therapies were reviewed to ensure subject fulfillment of inclusion/exclusion criteria. Subjects were advised to refrain from any therapy that was non-compliant with the inclusion/exclusion criteria. Any new or modified therapies during the study were recorded and evaluated as a possible cause for any AE occurrence.

During the study, subjects were allowed to continue their routine cleansing regimen but encouraged to avoid vigorous scrubbing of SKTLs, avoid excessive natural or artificial ultraviolet radiation and encouraged to sunscreen on SKTLs.

The following medications and treatments were not permitted during the study:

- Destructive therapies including but not limited to LASER, light or other energy based therapy, liquid nitrogen, electrodessication, curettage, microdermabrasion, chemical peels

- Topical and systemic medications with anti-inflammatory, destructive or keratinocyte modulating mechanisms, including but not limited to retinoids, glucocorticoids, anti-metabolites, antibiotics, 5-fluorouracil, ingenol mebutate, and imiquimod
- Avoid any topical products, except routine cleansing products, to the STKLs 12 hours prior to a treatment visit (Visits 2 and 4) and 6 hours after treatment
- Avoid washing and submerging SKTLs 6 hours after treatment

Safety Evaluation
The following safety assessments were performed:
- Vitals signs measured at screening, Visit 2 prior to initial treatment and Visit 8
- Urine pregnancy test for female subjects of childbearing potential was performed at screening, Visit 2 before initial treatment and Visit 8
- Laboratory evaluations: complete blood count and comprehensive chemistry panels were performed at screening and Visit 8
- LSR assessments by subject and investigator at Visit 2 prior to initial treatment as baseline assessment; after treatment at Visit 2 and Visit 4; prior to any treatment on Visit 4; and Visits 3 and 5-8
- Adverse event reporting done at each visit

Efficacy Evaluation
The **Primary Endpoint** was the proportion of subjects with clearance of all four SKTLs at Day 106 in comparison to Baseline.

Reviewer comment: The subject LSR assessments were completed 10 minutes (+/- 4 minutes) after IP application while the investigator LSR assessments were completed 20 minutes (+/- 4 minutes) after IP application. LSRs were reported as an AE only if the use of IP was interrupted or discontinued or if therapy was required to manage the AE.

Phase 3 Trial: A-101-SEBK-302 (SEBK-302)

Study Title: A randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of hydrogen peroxide (A-101) solution 40% in subjects with seborrheic keratosis on the trunk, extremities and face (study 2)

Study Period: January 28, 2016 to October 27, 2016

Study Objective: to evaluate the effectiveness of the to-be-marketed formulation of HP solution, 40% when applied to four SKTLs on the trunk, extremities and face compared with a matching vehicle solution

Study Design: This was a randomized, double-blind, vehicle-controlled, parallel group, multi-center study.

Number of Centers: 17 in the United States

Number of Subjects: 487 subjects randomized

Study Population
Key Inclusion and Exclusion Criteria: Inclusion and exclusion criteria for SEBK-302 was the same as trial SEBK-301.

Study Visits and Procedures
Overall design of SEBK-302 was the same as trial SEBK-301.

Safety Evaluation
Safety evaluation was the same as in trial SEBK-301.

Efficacy Evaluation
Primary and secondary endpoints were the same as in trial SEBK-301.

Reviewer comment: Trial SEBK-302 was identical in design to trial SEBK-301.

Phase 3 Study: A-101-SEBK-303 (SEBK-303)

Study Title: An open-label study of the safety of A-101 solution 40% in subjects with seborrheic keratosis on the trunk, extremities and face
Study Period: February 15, 2016 to November 2, 2016
Study Objective: to evaluate the safety of the to-be-marketed formulation of HP solution 40%
Study Design: This was an open label, multi-center study.
Number of Centers: 10
Number of Subjects: 147 subjects enrolled
Study Population
Key Inclusion and Exclusion Criteria: Inclusion and exclusion criteria for trial SEBK-303 was the same as trial SEBK-301 and SEBK-302.

Study Visits and Procedures
Overall design of trial SEBK-303 was the similar to the active arms of trials SEBK-301 and SEBK-302 with additional possible re-treatments on Day 43 and 63 for SKTLs with PLA $\geq$ 0 and additional visits for LSR assessments on Day 71, 92, 120 and 148.

Table 5: Study SEBK-303 Study Flow Chart

Visit	1	2	3	4	5	6	7	8	9	10	11	12
Day	-13 to 0	1	8	22	29	43	50	64	71	92	120	148
Informed consent	X											
Subject identifier	X											
Inclusion/exclusion criteria	X											
Demographics & medical history	X											
Vital signs	X	X[1]										X
Clinical laboratory sampling	X											X
Urine pregnancy tests	X	X[1]										X
Target lesion identification	X											
Physician's lesion assessment	X	X[1]		X[1]		X[1]		X[1]				X
Lesion dimensions	X											
Local skin reactions		X[2]	X	X[2]	X	X[2]	X	X[2]	X	X	X	X
Standardized photography	X	X[1]										X
Study medication assignment		X[1]										
Study medication treatment		X		X[3]		X[3]		X[3]				
Subject instructions	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X

[1] Performed prior to the study medication treatment
[2] Performed prior to and after completion of the study medication treatment
[3] Only for Target Lesions that meet the retreatment criteria.

Source: Applicant's submission; Protocol; A-101-SEBK-303; Section 5.2; Study Flow Chart, page 21.

Investigational Product

IP was applied to SKTLs in the same manner as in trials SEBK-301 and SEBK-302. In addition to treatment at Visit 2/Day 1, if an SKTL had a PLA $\geq$ 0 on Day 22, 43 or 64, the lesion was re-treated with IP.

Safety Evaluation

Safety evaluation was the same as in trial SEBK-301 and SEBK-302 with a longer duration of follow-up, up to Day 148.

The following safety assessments were performed:

- Vitals signs measured at screening, Visit 2 prior to initial treatment and Visit 12
- Urine pregnancy test for female subjects of childbearing potential was performed at screening, Visit 2 before initial treatment and Visit 12
- Laboratory evaluations: complete blood count and comprehensive chemistry panels were performed at screening and Visit 12
- Local skin reaction assessments by subject and investigator at Visit 2 prior to initial treatment as baseline assessment; after treatment at Visit 2, 4, 6 and 8; prior to treatment on Visit 4, 6 and 8; and Visits 3, 5, 7 and 9-12
- Adverse event reporting done at each visit

Efficacy Evaluation
This was an open-label study. As in trials SEBK-301 and SEBK-302, PLA was assessed at Visit 1/screening, Visit 2/Day 1 pre-treatment, Visit 4/Day 22 pre-treatment, Visit 6/Day 43 pre-treatment, Visit 8/Day 54 and Visit 12/Day 148.

Reviewer comment: This study was not an extension of the pivotal trials SEBK-301 and SEBK-302. There was no placebo- or vehicle-controlled arm in this study, and thus this study was not included in the pooled safety analysis.

Phase 2 Trial: A-101-SEBK-201 (SEBK-201)
Study Title: A randomized, double-blind, vehicle-controlled, within subject comparison study of the safety, tolerability and effectiveness of A-101 topical solution in subjects with seborrheic keratosis
Study Period: October 22, 2013 to February 25, 2014
Study Objective: to evaluate effectiveness, safety and tolerability of HP solution 25%, 32.5% and 40% applied to SKTLs on the back versus vehicle
Study Design: randomized, double-blind, vehicle-controlled, within-subject, single-site trial
Number of Centers: 1 study site in the US
Number of Subjects: 35 subjects enrolled (all subjects received all 4 IPs, for each subject, the SKTLs were randomized to IP
Study Population: adult subjects (18 years and older) with four SKTLs on the back
Study Visits and Procedures: rach subject received all four IPs, one to each SKTL on Day 1. Each SKTL could be re-treated with the same IP on Day 22 if the PLA $\geq$ 0.
Investigational Product: HP solution 25%, 32.5% and 40% and vehicle were applied to the lesion on Day 1. Multiple applications of the IP are applied approximately every 30 seconds to keep SKTLs wetted for a total of 5-6 minutes. If an SKTL had a PLA $\geq$ 0 on Day 22, the lesion was re-treated unless the SKTL:

- had a pre-treatment LSR grade of 3 for any sign or symptoms AND the grade increased compared to the previous visit
- was considered not appropriate for re-treatment by the investigator

Safety Evaluation: The following evaluations were performed: vital signs, hematology panel, comprehensive chemistry panel, urine pregnancy test, ECG, LSR assessments, AE monitoring, and photography of SKTLs.
Efficacy and Endpoint Measures: For each SKTL, the following was assessed: an investigator PLA grade, Subject's Self-Assessment (SSA) grade, and measurement of surface area and thickness.

Table 6: Physician Lesion Assessment used in Trial SEBK-201

Physician's Lesion Assessment	
Grade	Descriptor
0	Clear: no lesion, normal skin
1	Mild: lesion is barely evident on examination
2	Moderate: obvious lesion
3	Severe: severe lesion, prominent

Source: Applicant's submission; Protocol; A-101-SEBK-201; Section 6.1.2; PLA, page 34

Table 7: Subject's Self-Assessment used in Trial SEBK-201

Subject's Self-Assessment	
Grade	Descriptor
0	Clear: no lesion is noticeable
1	Mild: lesion is barely noticeable on careful examination, but is not obvious
2	Moderate: lesion is obvious on routine examination
3	Severe: lesion is prominent

Source: Applicant's submission; Protocol; A-101-SEBK-201; Section 6.1.1; SSA, page 34

Reviewer's comment: Similar to trials SEBK-301, SEBK-302 and SEBK-303, LSRs were reported as an AE only if the treatment with of IP was interrupted or discontinued or if therapy was required to manage the AE. In addition, any LSR that increased in severity compared to the Visit 2 pre-treatment assessment by 1 or more grades AND persisted for 2 or more successive visits were reported as an AE. The more restrictive definition for an LSR to be reported as an AE may lead to under-reporting of AEs even in this small trial population.

In addition to Phase 3 trials exclusion criteria, Phase 2 trials excluded individuals with history of hypertrophic or keloid scarring.

Phase 2 Trial: A-101-SEBK-202
Study Title: A randomized, double-blind, vehicle-controlled, parallel group study of the dose-response profile of A-101 solution in subjects with seborrheic keratosis
Study Period: June 16, 2014 to December 22, 2014
Study Objective: to evaluate dose-response relationship, safety and efficacy of HP solution 32.5% and 40% versus vehicle solution applied to SK Target lesions on the trunk and extremities
Study Design: randomized, double-blind, vehicle-controlled, parallel group, multi-center trial
Number of Centers: 5 in the US
Number of Subjects: 172 randomized
Study Population: adult subjects (18 years and older) with four SKTLs on the trunk and extremities

Study Visits and Procedures: This study was similar to trials SEBK-301 and -302 but did not include the face and did not require 1 lesion to be on an extremity.
Investigational Product: IP treatment was similar to trials SEBK-301 and -302.
Safety Evaluation: The following evaluations were performed: vital signs, hematology panel, comprehensive chemistry panel, urine pregnancy test, LSR assessments, AE monitoring, and photography of SK Target lesions.
Efficacy and Endpoint Measures: For each SK Target lesion, the following was assessed: an investigator PLA grade, Subject's Self-Assessment (SSA) grade, and measurement of surface area and thickness.

Table 8: Physician Lesion Assessment used in SEBK-202

Physician's Lesion Assessment	
Grade	Descriptor
0	Clear: no visible seborrheic keratosis lesion
1	Near Clear: a visible seborrheic keratosis lesion with a surface appearance different from the surrounding skin (not elevated)
2	Thin: a visible seborrheic keratosis lesion (thickness ≤1mm)
3	Thick: a visible seborrheic keratosis lesion (thickness >1mm)

Source: Applicant's submission; Protocol; A-101-SEBK-202; Section 6.1.2; PLA, page 36.

Table 9: Subject's Self-Assessment used in Trial SEBK-202

Subject's Self-Assessment	
Grade	Descriptor
0	None: no visible seborrheic keratosis lesion
1	Mild: a slightly raised, light brown seborrheic keratosis lesion
2	Moderate: an obvious raised, brown seborrheic keratosis lesion
3	Severe: a prominent rough, dark seborrheic keratosis lesion

Source: Applicant's submission; Protocol; A-101-SEBK-202; Section 6.1.1; SSA; page 36.

Reviewer's comment: Similar to trials A-101-SEBK-301, -302, -303 and -201, LSRs were reported as an AE only if the treatment with IP was interrupted or discontinued, or if therapy was required to manage the AE.

Phase 2 Trial: A-101-SEBK-203 (SEBK-203)
Study Title: A randomized, double-blind, vehicle-controlled, parallel group study of the dose-response profile of A-101 solution in subjects with seborrheic keratosis of the face
Study Period: September 5, 2014 to February 27, 2015
Study Objective: to evaluate dose-response relationship, safety and efficacy of HP solution 32.5% and 40% versus vehicle solution applied to SKTL on the face
Study Design: randomized, double-blind, vehicle-controlled, parallel group, multi-center trial

Number of Centers: 4 in the US
Number of Subjects: 119 randomized
Study Population: adult subjects (18 years and older) with one SKTL on the face
Study Visits and Procedures: This study was the same as trial SEBK-202 but the SKTLs were located only on the face.
Investigational Product: IP treatment was the same as in trials SEBK-301, SEBK-302, SEBK-303 and SEBK-201.
Safety Evaluation: The following evaluations were performed: vital signs, hematology panel, comprehensive chemistry panel, urine pregnancy test, LSR assessments, AE monitoring, and photography of SKTL (only at one chosen site). Any AE that requires use of the eyewash kit was reported as "eye irritation."
Efficacy and Endpoint Measures: For each SKTL, the following was assessed: an investigator PLA grade, SSA grade, and measurement of surface area and thickness. The scales for the PLA and SSA are the same used in trial SEBK-202.

Phase 2 Trial: A-101-SEBK-205 (SEBK-205)
Study Title: A within subject study of the bioavailability of A-101 topical solution administered under maximal use conditions in subjects with seborrheic keratosis
Study Period: May 9, 2016 to July 27, 2016
Study Objective: to assess whether treatment with HP solution 40%, under maximal use condition, will lead to an increase of endogenous levels of HP in the blood of subjects with SK on the trunk, extremities and face
Study Design: open-label, maximal use, single-site study
Number of Centers: 1 in US
Number of Subjects: 24 enrolled
Study Population: adults with 10 SKTLs on trunk, extremities and at least one on the face
Study Visits and Procedures: After screening visit, subject were confined to the investigational site for Visit 2 and 3. At Visit 2, baseline blood samples were obtained. At Visit 3, each subject received HP solution, 40% 10 SKTLs and had post-treatment blood samples drawn. Visit 4 and 5 included safety assessments.

Table 10: SEBK-205 Maximal Use Study Flow Chart

Visit	1	2	3		4	5
Day	N/A	Within 14 Days of Visit 1	1 (Within 7 days of Visit 2)		8	29
			Pre-treatment	Post-treatment		
Informed consent	X					
Subject identifier	X					
Inclusion/exclusion criteria	X	X				
Demographics & medical history	X					
Vital signs	X	X	X			X
Clinical laboratory sampling	X					X
Urine pregnancy tests	X		X			X
Target lesion identification	X					
Confirm target lesion locations			X	X	X	X
Target lesion dimensions	X					
Local skin reactions			X	X	X	X
Standardized photography	X					
No-treatment samples for GSH and GSSG determination		X[a]				
Weigh study medication			X	X		
Treatment samples for GSH and GSSG determination			X[b]	X[c]		
A-101 Solution 40% treatment				X		
Subject instructions	X	X	X	X	X	
Concomitant therapies	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

a Performed at 0, 0.75, 1, 1.5, 2.5, 4.5, and 6.5 hours.
b Performed at 0 hour, just prior to initiating the study medication treatment and performed so the 0-hour sample time was within ±30 minutes of the Visit 2 0-hour sample time
c Performed at 0.25, 0.5, 1, 2, 4, and 6 hours posttreatment

Source: Applicant's submission; Study Report Body; A-101-SEBK-205; Section 9.5.1.1; Schedule of Event and Procedures; page 23.

Investigational Product: IP was to-be-marketed HP solution, 40%. IP was applied to SKTLs using the applicator tip for approximately 20 seconds to ensure SKTL wetted with IP. SKTLs allowed to dry for 1 minute. Application repeated four times per SKTL.
Safety Evaluation: The following evaluations were performed: vital signs, hematology panel, comprehensive chemistry panel, urine pregnancy test, LSR average for SKTLs and AE monitoring.
Pharmacokinetic Assessment: Twelve men and twelve women were included. Pre-treatment baseline blood samples were drawn at Visit 2, and within 7 days, post-treatment blood samples were drawn at Visit 3. Whole blood glutathione (GSH) and glutathione disulfide (GSSG) levels were used as surrogates for blood HP levels. The applicant purports a decrease in GSH/GSSG from subject's baseline to post-treatment

measurements indicates an increase in systemic HP levels from topical application of HP.
Efficacy and Endpoint Measures: No efficacy endpoint measures were done.

Reviewer's comment: Although the face SKTL size may have included smaller (≤ 3mm wide and ≤ 15mm long) SK than in the pivotal trials SEBK-301 and SEBK-302 (≤ 5mm wide and ≤ 15mm long), there was a greater number of total lesions treated to compensate for the potential inclusion of smaller facial SK.

Phase 1 Trial A-101-RIPT-101 (RIPT-101)
Study Title: Repeat insult patch test
Study Period: July 11, 2016 to September 16, 2016
Study Objective: to assess the potential for HP solution 40% to induce contact sensitization by repetitive application to normal skin of healthy volunteers.
Study Design: dermal safety study with test products randomized to test sites on subject back
Number of Centers: 1 in US
Number of Subjects: 233 enrolled
Study Population: healthy adults
Study Visits and Procedures: This study was of typical repeat insult patch test design: three-week induction with two-week rest period followed by re-challenge. During the induction period, test products were applied to the back on Monday, Wednesday and Friday. A total of four test products were applied to each subject. HP solution 40% and vehicle were applied and dried without patching. The negative (white petrolatum) and positive (0.5% sodium laurel sulfate) controls were applied under semi-occlusive patches. After 48 hours, patches were removed and 5 minutes later assessed for skin reaction. The test products were re-applied using the same patching method as the initial application, at the same sites. If grade 3 (severe) or higher reaction observed, the patch site was moved. If grade 3 or higher reaction was observed at the second site, the patch was dropped from the remainder of the study. After the ninth application and assessment, a two-week rest period started followed by a re-challenge to the test products. Re-challenge used the same patching and grading methods used during the induction phase.

Table 11: RIPT-101 Schedule of Assessments

Procedures	Day -30 to 0	Day 0 (M)	Days 2,9,16 (W)	Days 4,11,18 (F)	Days 7,14 (M)	Day 21 (M)	2 week rest	Day 35 (M)	Day 37 (W)	Day 38 (Th)	Day 39 (F)
	Screening	Patch	Grade/Patch	Grade/Patch	Grade/Patch	Grade		Patch	Grade	Grade	Grade
Informed consent	x										
Inclusion/exclusion criteria	x	x									
Demographics/Medical History	x										
Urine Pregnancy Test (WoCBP)	x										x
Apply study product and patches		x	x	x	x			x			
Test product drying		x	x	x	x			x			
Remove patches			x	x	x	x			x		
Evaluate test sites			x	x	x	x			x	x	x
Concomitant therapies		x	x	x	x	x		x	x	x	x
Adverse events		x	x	x	x	x		x	x	x	x

Source: Applicant's submission; Protocol; A-101-RIPT-101; Section V; Procedures; page 9.

Safety Evaluation: LSR at patch sites were evaluated by the investigator 5 minutes after patch removal using a five-point scale reproduced below. If a patch was dropped due to grade 3 or higher LSR on two occasions, the test sites continued to be evaluated till the end of the study.

Table 12: Skin Reaction Grading Scale used in RIPT-101

0 = No sign of irritation
1 = Slight erythema
2 = Noticeable erythema with slight infiltration
3 = Erythema with marked edema
4 = Erythema with edema and blistering

Other signs of skin reactions to the test products, such as dryness, cracking, peeling, etc., will be noted as comments.

Source: Applicant's submission; Protocol; A-101-RIPT-101; Section V; Procedures; page 7.

6 Review of Efficacy

Efficacy Summary

The primary evidence of efficacy was based on two well-controlled Phase 3 trials of similar design (A-101-SEBK-301 [SEBK-301] and A-101-SEBK-302 [SEBK-302]). Two Phase 3 trials were randomized, double-blind, vehicle-controlled, parallel-group, multicenter trials evaluating the safety and efficacy of hydrogen peroxide (HP) solution 40% applied up to two times three weeks apart for the treatment of seborrheic keratosis (SK) that are raised on the face, trunk and extremities in adults.

The two trials randomized 937 subjects, 18 years of age and older, who had four SK target lesions (SKTLs) with at least one SK target lesion (SKTL) on the face and one SKTL on the extremities. Subjects had each SKTL treated in clinic by a staff member

with four applications of HP solution 40%, separated by one minute drying time. If the SKTL was still present at the three-week follow-up visit, the SKTL could be re-treated in the same manner.

The primary endpoint was the proportion of subjects with clearance of all SKTLs (PLA = 0) at Visit 8/Day 106. In SEBK-301, 4% of HP solution, 40% treated subjects and 0% of vehicle treated subjects achieved clearance of all four SKTLs, a treatment effect of 4% ($p < 0.001$). In SEBK-302, 8% of HP solution, 40% treated subjects and 0% of vehicle treated subjects achieved clearance of all four SKTLs, a treatment effect of 8% ($p < 0.001$).

A major secondary endpoint was the proportion of subjects who achieved clearance of three or more SKTLs at Day 106 compared to baseline. In SEBK-301, 13% of HP solution, 40% treated subjects and 0% of vehicle treated subjects achieved clearance of three or more STKLs ($p < 0.001$) while in SEBK-302, 23% of HP solution, 40% treated subjects and 0% of vehicle treated subjects achieved clearance of three or more SKTLs ($p < 0.001$).

SKTLs on the face had a higher clearance rate than SKTLs on the trunk or extremities. SKTLs that were smaller or thinner at baseline were slightly more likely to achieve clearance than lesions that were larger or thicker.

Efficacy was consistent across sub-groups (by age, gender, race, ethnicity). In SEBK-302, nearly half of responders were from one site. Exclusion of this high responder site in analysis still led to clinical significance of the primary and secondary efficacy endpoints.

In this NDA, in two Phase 3 trials, the applicant showed that HP solution, 40% was effective in the treatment of SK that are raised on the face, trunk and extremities.

6.1 Indication

The applicant’s proposed indication is for the treatment of SK lesions.

6.1.1 Methods

The applicant is relying on two Phase 3 trials, SEBK-301 and SEBK-302, to provide evidence of efficacy to support approval. The intent to treat population (ITT) was used as the efficacy analysis population.

Table 13: Analysis sets

Population	HP 40%		Vehicle	
	SEBK-301	SEBK-302	SEBK-301	SEBK-302
Randomized	223	244	227	243
Safety population	223	244	227	243
Intent to treat population	223	244	227	243
Per protocol population	218	233	221	236

Source: Agency generated

6.1.2 Demographics

Baseline characteristics of the study population are presented in the tables below. Overall, baseline demographics were similar across the study arms. Subjects were predominantly White (99% and 97%, HP 40% and vehicle, respectively) and 56 years of age and older (98% and 94%, HP 40% and vehicle, respectively). These demographic characteristics are consistent with that patient population with SKs[1, 2]. The locations of lesions, Fitzpatrick skin types, and Physician Lesion Assessment (PLA) grade were similar between treatment arms and between the studies.

Table 14: Baseline Demographic Characteristics – ITT population (301 and 302)

	Study 301		Study 302	
	HP 40% N=223	Vehicle N=227	HP 40% N=244	Vehicle N=243
Age (years)				
Mean	68.3	69.1	68.4	69.1
Range	45-90	42-90	45-91	46-90
18 to 55 years	16 (7%)	15 (7%)	18 (7%)	15 (6%)
56 to 70 years	115 (52%)	115 (51%)	129 (53%)	123 (51%)
71 + years	92 (41%)	97 (43%)	97 (40%)	105 (43%)
Gender				
Female	138 (62%)	126 (56%)	148 (61%)	136 (56%)
Male	85 (38%)	101 (44%)	96 (39%)	107 (44%)
Race				
White	219 (98%)	221 (97%)	241 (99%)	236 (97%)
Black or African American	1 (<1%)	1 (<1%)	3 (1%)	3 (1%)
Am. Ind./ AK Native	--	--	--	1 (<1%)
Asian	2 (1%)	4 (2%)	--	2 (1%)
Native HI/ Pacific Islander	--	--	--	--
Other	1 (<1%)	1 (<1%)	--	1 (<1%)
Ethnicity				
Hispanic or Latino	5 (2%)	5 (2%)	12 (5%)	14 (6%)
Not Hispanic or Latino	214 (96%)	216 (95%)	229 (94%)	22 (91%)
Not Reported	4 (2%)	6 (3%)	3 (1%)	7 (3%)

Source: From Agency Statistics Review. (From pg. 38 of Study A-101-SEBK-301 Study Report Body and pg. 39 of Study A-101-SEBK-302 Study Report Body)

Pooled analysis of baseline demographic characteristics for trials SEBK-301 and SEBK-302 are presented in table below.

Table 15: Baseline Demographic Characteristics, 301 and 302 (Pooled)

Demographic Parameters	HP 40% (N=467) n (%)	Vehicle (N=470) n (%)
Sex		
Male	181 (39%)	208 (44%)
Female	286 (61%)	262 (56%)
Age		
Mean years (SD)	68.3 (9%)	69.1 (9%)
Median (years)	68	69
Min, Max (years)	45, 91	42, 90
Age Group		
>= 18 <= 55	34 (7%)	30 (6%)
>= 56 <= 70	244 (52%)	238 (51%)
>= 71	189 (41%)	202 (43%)
Race		
White	460 (99%)	457 (97%)
Black	4 (1%)	4 (1%)
Asian	2 (<1%)	6 (1%)
American Indian	0	1 (<1%)
Native Hawaiian	0	0
Other	1 (<1%)	2 (<1%)
Missing Race	0	0
Ethnicity		
Hispanic	17 (4%)	19 (4%)
Non-Hispanic	443 (95%)	438 (93%)
Missing Ethnic	7 (2%)	13 (3%)
Region		
United States	467 (100%)	470 (100%)

Source: Agency generated.

Baseline by Fitzpatrick skin type, SKTL location and disease severity (PLA) were generally balanced across the treatment arms (Table 16 and 17).

Table 16: Baseline Demographic Characteristics in Respect to Fitzpatrick Skin Type (Pooled)

Fitzpatrick Skin Type	HP 40% N = 467 n (%)	Vehicle N = 470 n (%)
1	58 (12%)	60 (13%)
2	225 (48%)	213 (45%)
3	145 (31%)	139 (30%)
4	34 (7%)	52 (11%)
5	5 (1%)	5 (1%)
6	0	1 (<1%)

Source: Modified from applicant's submission, Module 5.3.5.3, ISE, Table 1.

Table 17: Baseline Disease Characteristics in Respect to Physician Lesion Assessment and Total Lesion Area

	Study 301		Study 302	
	HP N=223	Vehicle N=227	HP N=244	Vehicle N=243
Baseline PLA				
Mean	2.23	2.26	2.35	2.35
All PLA = 2	107 (48%)	111 (49%)	82 (34%)	81 (33%)
At least one PLA = 3	116 (52%)	116 (51%)	162 (66%)	163 (67%)
Total Lesion Area (mm^2)[a]				
Mean	244.7	238.8	255.9	252.1
Median	233	216	252.5	243
Range	100 - 507	105 - 646	115 - 491	100 - 556

[a] Sum of 4 target lesions longest length x longest perpendicular
Source: Agency Statistics review (From pg. 42 of Study A-101-SEBK-301 Study Report Body and pg. 43 of Study A-101-SEBK-302 Study Report Body and reviewer analysis.)

6.1.3 Subject Disposition

Table 18 below presents all subjects who received at least one treatment with study drug. A total of 937 subjects were randomized across the two studies: 470 subjects to HP solution, 40% and 467 to vehicle. Approximately 1% of subjects discontinued from SEBK-301 and 2% of subjects discontinued from SEBK-302. The main reasons for discontinuation was withdrawal of consent and loss to follow-up (2 in SEBK-301 and 5 in SEBK-302). In SEBK-301, one subject in each arm withdrew due to an adverse event (one was a serious adverse event), while no subjects withdrew due to adverse events in SEBK-302. In SEBK-302, one subject was discontinued due to "other" and two subjects were lost to follow-up.

Table 18: Disposition of Subjects - ITT population

	Study 301		Study 302	
	HP	**Vehicle**	**HP**	**Vehicle**
Subjects Randomized	223	227	244	243
Discontinued	3 (1%)	1 (<1%)	0	8 (3%)
Adverse event	1 (<1%)	1 (<1%)	--	--
Subject withdrew consent	2 (1%)	--	--	2 (1%)
Lost to follow-up	--	--	--	5 (2%)
Other	--	--	--	1 (<1%)

Source: From Agency Statistics Review. (from pg. 37 of Study A-101-SEBK-301 Study Report Body and pg. 37 of Study A-101-SEBK-302 Study Report Body.)

6.1.4 Analysis of Primary Endpoint(s)

The efficacy results of individual Phase 3 trials as well as pooled analysis will be discussed in this section. As previously stated, the primary efficacy endpoint for both Phase 3 trials was the proportion of subjects achieving clearance of all four SKTLs at Day 106. HP solution, 40% was statistically superior to vehicle ($p<0.001$) on the primary endpoint at Day 106. Table 19 presents the results of the analysis of the primary endpoint.

Because there was limited missing data and the 0% response rate of the vehicle arm, the multiple imputation analysis and the per protocol analysis results were very similar to the primary analysis using non-responder imputation. Table 20 presents the results of the sensitivity analyses.

Table 19: Proportion of Subjects Achieving Clearance of All Four SKTLs at Day 106; SEBK-301 and SEBK-302

Endpoint	**A-101-SEBK-301**		**A-101-SEBK-302**	
	Vehicle (N = 227)	**HP 40% (N = 223)**	**Vehicle (N = 243)**	**HP 40% (N = 244)**
Subjects with Clearance of All Four SKTLS	0 (0%)	9 (4%)	0 (0%)	19 (8%)
2-sided p-value	-	0.002	-	< 0.001

Source: Modified from applicant' submission; 2.7.2 Summary of Clinical Efficacy; Table 10; page 31.

Table 20: Sensitivity Analyses for Complete Clearance at Day 106

	Study 301			Study 302		
	Hyd. Per. N=223	**Vehicle N=227**	**P-value**	**Hyd. Per. N=244**	**Vehicle N=243**	**P-value**
Per Protocol	9/218 (4%)	0/221 (0%)	0.002	19/233 (8%)	0/236 (0%)	<0.001
Multiple Imputation	9/223 (4%)	0/227 (0%)	0.002	19/244 (8%)	0/243 (0%)	<0.001

Source: From Agency Statistics review (from pg. 40 of Study A-101-SEBK-301 Study Report Body and pg. 40 of Study A-101-SEBK-302 Study Report Body.)

Reviewer's comment: *The applicant demonstrated that HP solution, 40% was statistically superior to vehicle for clearance of all four SKTLs compared to baseline, in both Phase 3 clinical trials. Sensitivity analyses support the results of the primary analysis.*

6.1.5 Analysis of Secondary Endpoints(s)

The major secondary endpoint in both Phase 3 trials was the proportion of subjects achieving clearance of three of four SKTLs at Day 106 compared to baseline. HP40% solution was statistically superior to vehicle (p<0.001), as presented in the table below.

Table 21: Proportion of Subjects Achieving Clearance of Three of Four SKTLs at Day 106; SEBK-301 and SEBK-302

Endpoint	**A-101-SEBK-301**		**A-101-SEBK-302**	
	Vehicle (N = 227)	**HP 40% (N = 223)**	**Vehicle (N = 243)**	**HP 40% (N = 244)**
Subjects Achieving Clearance of 3 of 4 SKTLs	0 (0%)	30 (14%)	0 (0%)	56 (23%)
2-sided p-value	-	< 0.001	-	< 0.001

Source: Modified from applicant' submission; 2.7.2 Summary of Clinical Efficacy; Table 11; page 33,

Reviewer's comment: The applicant demonstrated that HP solution, 40% was statistically superior to vehicle measured as clearance of three of four SKTLs, in both Phase 3 trials.

Conclusion: The secondary endpoint results support the primary endpoint results. The applicant has demonstrated that HP solution, 40% was superior to vehicle in the treatment of SKs that are raised on the face, trunk and extremities in adults.

6.1.6 Other Endpoints

The applicant also evaluated the following exploratory endpoints:

- Proportion of per-protocol subjects achieving PLA ≤ 1 at Day 106 compared to baseline
- In the per-protocol population, the average per-subject percent of lesions clear

The results are summarized in the table below:

Table 22: Additional Efficacy Analyses Completed by the Applicant

Endpoint	**A-101-SEBK-301**		**A-101-SEBK-302**	
	Vehicle (N = 221)	**HP 40% (N = 218)**	**Vehicle (N = 236)**	**HP 40% (N = 233)**
Proportions with PLA ≤ 1for all 4 target lesions in PP population	8 (4%)	33 (15%)	2 (1%)	67 (29%)
2-sided p-value	-	< 0.001	-	< 0.001
PLA average per-subject percent of lesions clear in PP population	1.9 (8%)	25.2 (29%)	0.6 (5%)	34.2 (33)
2-sided p-value	-	< 0.001	-	< 0.001

Source: Modified from applicant' submission; 2.7.2 Summary of Clinical Efficacy; Table 11; page 33.

6.1.7 Subpopulations

For the proportion of subjects achieving clearance of all four SKTLs on Day 106, the applicant evaluated the following subgroups: demographic characteristics (gender, race, age, ethnicity), baseline disease characteristics (baseline PLA, lesion area) and retreatment on Day 22.

Treatment effect was generally consistent across age groups, gender, race and ethnicity. Nearly all subjects were White and not Hispanic or Latino. All subjects were from the United States. See table below.

Table 23: Complete Clearance Rate by Subgroup Populations

	Study 301		Study 302	
	HP N=223	**Vehicle N=227**	**HP N=244**	**Vehicle N=243**
Age (years)				
18 to 55	0/16 (0%)	0/15 (0%)	2/18 (11%)	0/15 (0%)
56 to 70	5/115 (4%)	0/115 (0%)	12/129 (9%)	0/123 (0%)
71 +	4/92 (4%)	0/97 (0%)	5/97 (5%)	0/105 (0%)
Gender				
Male	2/85 (2%)	0/101 (0%)	6/96 (6%)	0/107 (0%)
Female	7/138 (5%)	0/126 (0%)	13/148 (9%)	0/136 (0%)
Race				
White	9/219 (4%)	0/221 (0%)	19/241 (8%)	0/236 (0%)
Black or African-American	0/1 (0%)	0/1 (0%)	0/3 (0%)	0/3 (0%)
Asian	0/2 (0%)	0/4 (0%)	--	0/2 (0%)
Am. Ind./ AK Native	--	--	--	0/1 (0%)
Other	0/1 (0%)	0/1 (0%)	--	0/1 (0%)
Ethnicity				
Hispanic or Latino	0/5 (0%)	0/5 (0%)	1/12 (8%)	0/14 (0%)
Not Hispanic or Latino	9/214 (4%)	0/216 (0%)	18/229 (8%)	0/222 (0%)
Not Reported	0/4 (0%)	0/6 (0%)	0/3 (0%)	0/7 (0%)

Source: From Agency Statistics review (Reviewer analysis).

The majority of subjects had at least 3 SKTLs retreated on Day 22. In SEBK-301, 1 subject had all SKTLs with PLA = 0 on Day 22, and thus did not need retreatment. On Day 106, 2 of the 4 lesions remained clear. In SEBK-302, 6 subjects had all 4 SKTLs with PLA = 0, and thus did not need retreatment. All 6 subjects remained clear at Day 106 and considered responders. See table below.

Table 24: Complete Clearance Rate by Number of Treatments

	Study 301		Study 302	
	HP N=223	**Vehicle N=227**	**HP N=244**	**Vehicle N=243**
1 or 2 lesions retreated	4/12 (33%)	--	3/18 (17%)	--
3 or 4 lesions retreated	5/206 (2%)	0/227 (0%)	10/220 (5%)	0/239 (0%)
Not retreated (all PLA=0 at Day 22)	0/1 (0%)	--	6/6 (100%)	--
Not retreated for other reasons	0/4 (0%)	--	--	0/4 (0%)

Source: From Agency Statistics review (from pg. 43 of Study A-101-SEBK-301 Study Report Body and pg. 44 of Study A-101-SEBK-302 Study Report Body and reviewer analysis)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only HP solution, 40% applied four times in one treatment session, with possible retreatment at Day 22, was evaluated in the Phase 3 trials. No additional analysis regarding other doses or dosing regimens could be performed.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The applicant did not evaluate persistence of lesion clearance following treatment.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues or analyses were identified.

In SEBK-302 and SEBK-302, relatively few subjects had complete clearance of all SKTLs by Day 106. Table 25 presents the number subjects with 0, 1, 2, 3, and 4 lesions clear on Day 106. HP 40% treated subjects had a mean of 1-1.4 lesions clear compared to a mean 0.2-0.07 lesions clear when treated with vehicle.

Table 25: Number of Cleared Lesions at Day 106 (Subject Level)

	Study 301		**Study 302**	
# lesions clear	**HP 40% N=223**	**Vehicle N=227**	**HP 40% N=244**	**Vehicle N=243**
4	9 (4.0%)	0 (0%)	19 (8%)	0 (0%)
3	21 (10%)	0 (0%)	37 (15%)	0 (0%)
2	29 (13%)	4 (2%)	47 (19%)	1 (<1%)
1	68 (31%)	9 (4%)	51 (21%)	4 (2%)
0	93 (42%)	213 (94%)	90 (37%)	231 (95%)
Missing	3 (1%)	1 (<1%)	0 (0%)	7 (3%)
Mean # lesions clear	1.0	0.07	1.4	0.02

Source: From Agency Statistics review (Reviewer analysis).

SEBK-301 had 9 subjects with complete clearance of SKTLs across 7 centers. SEBK-302 had 10 of 19 subjects with complete clearance of SKTLs from 1 center (Center 14) while the remaining 9 responders were from 5 centers. Analysis excluding the high responder site in SEBK-302 are similar to the results of SEBK-301 and remain statistically significant. See table below.

Table 26: Complete Clearance Rate at Day 106 in Study SEBK-302 Excluding Center 14

	Study 302		
	HP 40%	**Vehicle**	**P-value**
All Centers Except Center 14	9/223 (4.0%)	0/221 (0%)	0.002
Center 14	10/21 (48%)	0/22 (0%)	

Source: Agency Statistics review (Reviewer analysis.)

In SEBK-301 and SEBK-302, each subject had 4 SKTLs received study treatment. Overall, 26% of SKTLs treated with HP40% in SEBK-301 and 34% of SKTLs treated with HP 40% in SEBK-302 cleared. Facial SKTLs had the highest rate of clearance followed by SKTLs on the trunk and extremities. Thin lesions (PLA = 2) were more likely to clear than thick lesions (PLA = 3), and SKTLs smaller than median size were more likely to clear than SKTLs greater than median size. See Table 27 and 28 below.

Table 27: SKTL Clearance Rates by Body Location (Lesion Level)

	Study 301		Study 302	
	HP 40% N=879	**Vehicle N=903**	**HP 40% N=976**	**Vehicle N=944**
Overall	225/879 (26%)	17/903 (2%)	332/976 (34%)	6/944 (<1%)
Face	97/263 (37%)	10/278 (4%)	146/305 (48%)	4/276 (1%)
Trunk	114/502 (23%)	5/521 (1%)	165/583 (28%)	2/573 (<1%)
Extremities	14/114 (12%)	2/104 (2%)	21/88 (24%)	0/95 (0%)

Source: Agency Statistics review (Reviewer analysis.)

Table 28: SKTL Clearance Rates by Baseline PLA and Lesion Area (Lesion Level)

	Study 301		Study 302	
	HP 40% N=879	**Vehicle N=903**	**HP 40% N=976**	**Vehicle N=944**
Baseline PLA				
PLA=2	185/677 (27%)	13/674 (2%)	228/635 (36%)	5/609 (1%)
PLA=3	40/202 (20%)	4/229 (2%)	104/341 (31%)	1/335 (<1%)
Baseline Area				
≤ Median[a]	130/446 (29%)	11/478 (2%)	174/473 (37%)	5/494 (1%)
> Median	95/433 (22%)	6/425 (1%)	158/503 (31%)	1/450 (<1%)

[a] Baseline median of the lesion area across both treatment arms was 49 mm^2 in Study 301 and 55 mm^2 in Study 302.
Source: Agency Statistics review (Reviewer analysis.)

Reviewer comment: SKs on the face are more likely to be thinner and smaller than SKs on the trunk and extremities which is supported by the above findings of greater efficacy

noted in SKTLs on the face, SKTLs with baseline PLA=2, and SKTLs with baseline area smaller than the median.

For further details on the analysis for efficacy, we refer the statistical review by Dr. Kathleen Fritsch.

7 Review of Safety

Safety Summary

7.1 Methods

The assessment of safety for hydrogen peroxide (HP) 40% solution was based on analysis of data from two Phase 3 trials (SEBK-301 and SEBK-302.) The safety population included 467 subjects who were randomized and received at least one treatment. 91% of subjects in the HP solution, 40% group received repeat treatment of 3 or 4 SKTLs, at Visit 4/Day 22 compared to 99% of subjects in the vehicle group. A Phase 3 open-label study (A-101-SEBK-303 [SEBk-303]) included 147 subjects with up to 4 total treatments with HP solution, 40%.

During the development of HP for the seborrheic keratosis (SK) indication, a total of 769 adult subjects (18-97 years of age) with SKs were exposed to at least one treatment with HP solution, 40%. The exposure to HP solution, 40%, with regards to the size of the safety database and the number of treatments, was adequate for evaluation of safety for the indication of treatment of SK that are raised on the face, trunk and extremities in adult patients.

During the HP solution, 40% development program, one death was reported (SEBK-203). Detailed analysis of this event did not suggest causal relationship (refer to section 7.3.1).

In the safety population, 10 subjects who received HP40% solution had 14 serious adverse events (SAEs) while 10 subjects who received vehicle had 11 SAEs. One subject in each arm discontinued study drug due to an SAE. No SAE was considered drug related, and review of these SAE cases did not reveal safety signals (refer to section 7.3.2).

The most frequently reported adverse reactions were local skin reactions (LSR), particularly for the symptoms of pruritus and stinging and signs of erythema, stinging, edema, scaling, crusting and pruritus (refer to section 7.4.1).

Laboratory evaluations (hematology and comprehensive chemistry panels) were monitored during conduct of Phase 2/3 trials. No clinically significant abnormalities were noted (refer to section 7.4.2) in Phase 3 trials.

Vitals signs (blood pressure, pulse, and body temperature) were monitored during conduct of Phase 2/3 trials. No clinically significant differences from baseline to Day 106 or trends of abnormalities were identified (refer to section 7.4.3) in Phase 3 trials.

ECGs were not done in Phase 3 studies and the applicant submitted a thorough QT (TQT) study waiver based on the results of SEBK-205 (increased systemic exposure could not be measured after HP solution, 40% applied under maximal use conditions). Review of the applicant's justification and lack of cardiovascular signal in early development support not requiring TQT study for HP solution, 40% (refer to section 7.4.4).

In this reviewer's opinion, the applicant provided adequate evidence of safety of HP solution, 40% and no safety signals that would preclude an approval were identified. REMS is not recommended for this product.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database primarily consists of two Phase 3 trials, SEBK-301 and SEBK-302. These trials were chosen as the focus of the safety review due to their similarity of study design; enrolled subjects were the targeted patient-population for proposed indication; and the treatment was at doses that reflect anticipated use (single treatment with possible repeat treatment of raised SK on common treatment locations).

Safety was also derived from the open-label Phase 3 trial, SEBK-303, with up to 4 total treatments, and Phase 1/2 trials that assessed safety of HP 40% during the development program for the SK indication.

7.1.2 Categorization of Adverse Events

The coding of AEs using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system Version 19.0 terminology appeared adequate and allowed for accurate estimation of AE risks.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The primary focus of this safety review will be data from two Phase 3 trials (SEBK-301 and SEBK-302). Data from these two trials will be pooled together to compare incidences of AEs. These studies were chosen as the focus of the safety review because of the similarity of design and enrolled subjects, large number of subjects, vehicle-controlled treatment, and the HP solution doses and dosing regimen reflect anticipated use. Data obtained during the vehicle-controlled trials allowed direct comparison of AE rates in HP solution treated subjects to rates of AEs in vehicle treated

subjects. Data from the non-controlled Phase 3 trial were used to assess the potential safety signals that may occur at later time points following repeat treatments, up to four total treatments, with HP solution. However, data from non-controlled trials is difficult to interpret due to lack of a comparison arm.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

During the development of HP for the SK indication, a total of 769 adult subjects (18-97 years of age) were exposed to at least one treatment with HP solution, 40%. Another 96 subjects received at least one treatment with HP 32.5% solution.

In SEBK-301 and SEBK-302, at Day 22, more than 90% of subjects had 3 or 4 SKTLs retreated, 6% of subjects had 1 or 2 SKTLs retreated, and approximately 2% did not receive the second treatment (due to complete clearance on Day 22, dropout or otherwise did not receive treatment). See table below.

Table 29: Extent of Exposure in SEBK-301 and SEBK-302

	Study 301		**Study 302**	
	HP N=223	**Vehicle N=227**	**HP N=244**	**Vehicle N=243**
Baseline				
4 lesions treated	223 (100%)	227 (100%)	244 (100%)	243 (100%)
Day 22				
1 or 2 lesions retreated	12 (5%)	--	18 (7%)	--
3 or 4 lesions retreated	206 (92%)	227 (100%)	220 (90%)	239 (98%)
Not retreated	5 (2%)	--	6 (2%)	4(2%)

Source: Agency Statistics review (reviewer analysis.)

Overall exposure to HP solution, in terms of dose, frequency and duration of dosing, and the target population was adequate for evaluation of safety.

Table 30: Overall Exposure of Subjects with SKs to Hydrogen Peroxide 40% solution

Study	Vehicle	A-101 Solution	
		32.5%	40%
SEBK-205 – 10 target lesions/subject (within-subject design), 1 treatment	24	NA	24
SEBK-201 – 1 target lesion/study drug (within-subject design), 2 treatments	35	35	35
SEBK-202 – 4 target lesions/subject, up to 2 treatments	58	57	57
SEBK-203 – 1 target lesion/subject, up to 2 treatments	41	39	39
SEBK-301 – 4 target lesions/subject, up to 2 treatments	227	NA	223
SEBK-302 – 4 target lesions/subject, up to 2 treatments	243	NA	244
SEBK-303 – 4 target lesions/subject, up to 4 treatments	NA	NA	147
Total Subjects with SKs	628	131	769

Source: Modified from applicant's submission, Module 5.3.5.3. ISS, Table 3, page 20.

Table 31 presents the baseline demographic characteristics for SEBK-301, SEBK-302 and SEBK-301/SEBK-302 pooled safety population. Most subjects were White (97.2%), female (55.7%), and age 56 and older (93.6%). The study population was consistent with the population of patients with SK in the US.[1, 2]

Table 31: Baseline Demographic Characteristics by Trial for SEBK-301 and SEBK-302

	SEBK-301		SEBK-302		Pooled	
	HP 40% N = 223	Vehicle N = 227	HP 40% N = 244	Vehicle N = 243	HP 40% N = 467	Vehicle N = 470
Sex						
Male	85 (38%)	101 (45%)	96 (39%)	107 (44%)	181 (39%)	208 (44%)
Female	138 (62%)	126 (56%)	148 (61%)	136 (56%)	286 (61%)	262 (56%)
Age						
Mean years (SD)	68.3	69.1	68.4	69.1	68.3	69.1
Median (years)	69	69	68	69	68	69
Min, Max (years)	45, 90	42, 90	45, 91	46, 90	45, 91	42, 90
Age Group						
>= 18 <= 55	16 (7%)	15 (7%)	18 (7%)	15 (6%)	34 (7%)	30 (6%)
>= 56 <= 70	115 (52%)	115 (51%)	129 (53%)	123 (51%)	244 (52%)	238 (51%)
>= 70	92 (41%)	97 (43%)	97 (40%)	105 (43%)	189 (41%)	202 (43%)
Race						
White	219 (98%)	221 (97%)	241 (99%)	236 (97%)	460 (99%)	457 (97%)
Black	1 (<1%)	1 (<1%)	3 (1%)	3 (1%)	4 (1%)	4 (1%)
Asian	2 (1%)	4 (2%)	0	2 (1%)	2 (<1%)	6 (1%)
American Indian	0	0	0	1	0	1 (<1%)
Native Hawaiian	0	0	0	0	0	0

Other	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)	2 (<1%)
Missing Race	0	0	0	0	0	0
Ethnicity						
Hispanic	5 (2%)	5 (2%)	12 (5%)	14 (6%)	17 (4%)	19 (4%)
Non-Hispanic	214 (96%)	216 (95%)	229 (94%)	222 (91%)	443 (95%)	438 (93%)
Missing Ethnicity	4 (2%)	6 (3%)	3 (1%)	7 (3%)	7 (2%)	13 (3%)
Fitzpatrick Skin Type						
Skin Type 1	37 (8%)	35 (8%)	21 (4%)	25 (5%)	58 (6%)	60 (6%)
Skin Type 2	108 (24%)	103 (23%)	117 (24%)	110 (23%)	225 (24%)	213 (23%)
Skin Type 3	62 (14%)	61 (14%)	83 (17%)	78 (16%)	145 (16%)	139 (15%)
Skin Type 4	14 (3%)	26 (6%)	20 (4%)	26 (5%)	34 (4%)	52 (6%)
Skin Type 5	2 (<1%)	2 (<1%)	3 (1%)	3 (1%)	5 (1%)	5 (1%)
Skin Type 6	0	0	0	1 (<1%)	0	1 (<1%)

Source: Agency generated

Reviewer's comment: The baseline demographic characteristics of subjects across trials SEBK-301 and SEBK-302 and across treatment arms are similar. Although trial SEBK-302 has approximately twice as many self-identified Hispanics (5% and 6%, HP 40% and vehicle, respectively) compared to trial SEBK-301 (2% for both arms,) the proportions of Fitzpatrick skin types are similar across the treatment arms and trials.

The SKTLs location and baseline disease severity (Physician Lesion Assessment [PLA]) are similar between the vehicle and HP solution, 40% treated subjects as shown in Tables 32 and 33, respectively.

Table 32: Baseline Demographic Characteristics in Respect to SKTL Location (Pooled)

SKTL Location	**HP 40% n[a]**	**Vehicle n**
Total SKTLs	1868	1880
Extremities	206 (11%)	203 (11%)
Face	571 (31%)	563 (30%)
Trunk	1091 (58%)	1114 (59%)

a Percentages are based on the total number of lesions from 3 locations within each treatment group.
Source: Modified from applicant submission, Module 5.3.5.3, ISS, Table 2.1.

Table 33: Baseline Demographic Characteristics in Respect to Physician Lesion Assessment Score (Pooled)

SKTL Location	**HP 40% N = 467**	**Vehicle N = 470**
Low (All PLA = 2)	189 (41%)	192 (41%)
High (All PLA = 3)	16 (3%)	36 (8%)
Other (not High or Low)	262 (56%)	242 (52%)

a. SKTL inclusion criteria requires PLA of 2 or more at baseline.
Source: Modified from applicant's submission, Module 5.3.5.3. ISE, Table 2.

Reviewer's comment: The pooled vehicle group had twice as many subjects with high severity PLA (All SKTL PLA = 3) (8% versus 3% in the HP 40% arm). Thicker lesions may be more difficult to treat, and thus may be less likely to clear than thinner lesions.

7.2.2 Explorations for Dose Response

The HP dose response evaluation was conducted in Phase 2 trials: SEBK-201, SEBK-202, and SEBK-203. The applicant selected the 40% dose based on the results of a within-subject comparison study, trial SEBK-201, where 35 subjects with SKs had at least four SKTLs on the back. Each SKTL was randomized to receive a different treatment: vehicle, HP 25% solution, 32.5% solution, or 40% solution. At Day 22, the lesions were re-treated with the same treatment as on Day 1 if the PLA grade was greater than 0. The primary endpoint was a mean change in PLA at Visit 9/Day 78 compared to baseline PLA at Visit 2/Day1, prior to initial treatment. A statistically greater proportion of PLA responders, subjects with PLA grade 0 at Visit 9/Day 78, was found for HP 32.5% (15%; p = 0.0202) and HP 40% (32%, p = 0.0003), but not for HP 25%. These results demonstrate a dose response. Safety evaluation did not reveal safety signals for HP 25% or 32.5% solution. Based on the efficacy and safety results, the applicant selected HP solution, 40% dose as the one with the best benefit-risk profile and conducted Phase 3 trials using this dose.

7.2.3 Special Animal and/or In Vitro Testing

The applicant did not conduct any special animal of in vitro testing.

7.2.4 Routine Clinical Testing

Routine safety monitoring included clinical evaluation and laboratory testing at specified time points. The following safety monitoring was performed:

- Vital signs, including temperature, pulse and blood pressure
- Physical examination, including active assessments for local skin reactions and hair discoloration

- Laboratory evaluations: Complete blood count with white blood cell differential, comprehensive chemistry panel, urine pregnancy testing
- 12-lead echocardiogram (only SEBK-205)

Overall, safety monitoring performed during the conduct of trials supporting this NDA was appropriate and adequate for evaluation of safety of HP solution, 40%.

7.2.5 Metabolic, Clearance, and Interaction Workup

No studies on the distribution, metabolism and excretion of HP were conducted by the applicant. Discussion of the drug metabolism, clearance and drug-drug interaction is presented in section 4.4 Clinical Pharmacology of this review and the review by Dr. Yanhui Liu.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Based on possible mechanism of action, the applicant monitored AE of special interest local skin reactions and hair discoloration.

7.3 Major Safety Results

7.3.1 Deaths

Phase 3 Trials (SEBK-301 and SEBK-302)
No deaths were reported in two Phase 3 trials.

Phase 2 Trials and Open-label Phase 3 trial (SEBK-303)
No deaths were reported in trials SEBK-201, SEBK-202, and SEBK-303.

During the Phase 2 trial SEBK-203, one death (metastatic carcinoma of unknown primary) was reported. Discussion of this AE is presented below.

Subject #03-005 was a 56 years old Asian male who was enrolled in the study with a stable, clinically typical SK lesion on the left cheek at the screening visit on 24 September 2014. Past medical history included gastroesophageal reflux disease including treatment with sucralfate and pantoprazole. He had no other remarkable medical or surgical history. Visits 1 – 5 were completed satisfactorily. When the subject failed to return for Visit 6, the trial site contacted the subject's wife who informed the trial site that the subject was diagnosed with metastatic carcinoma of unknown primary. The subject expired on 29 November, 2014. The trial site was unable to obtain a copy of the death certificate. The investigator considered this death not to be related to HP solution, 40%.

Reviewer comment: The temporal relationship of the death to the treatment and the mechanism of action for HP does not support a causal relationship.

7.3.2 Nonfatal Serious Adverse Events

Phase 3 Trials (SEBK-301 and SEBK-302)
In two Phase 3 trials, 10 subjects who received HP solution, 40% experienced 14 SAEs while 10 subjects who received vehicle experienced 11 SAEs. One subject in each arm discontinued study drug due to an SAE (CNS lesion in HP 40% arm, ischemic stroke in vehicle arm). No SAE was considered drug related, and review of these SAEs did not reveal safety signals.

Table 34: Non-fatal Serious Adverse Events for Trials SEBK-301 and SEBK-302

Preferred Term	**HP 40% (N = 467) n (%)**	**Vehicle (N = 470) n (%)**
Anxiety	1 (0.2%)	0
Central nervous system lesion	1 (0.2%)	0
Coronary arterial stent insertion	1 (0.2%)	0
Dementia	1 (0.2%)	0
Intervertebral disc disorder	1 (0.2%)	0
Post-traumatic stress disorder	1 (0.2%)	0
Precerebral artery occlusion	1 (0.2%)	0
Pubis fracture	1 (0.2%)	0
Pulmonary contusion	1 (0.2%)	0
Pulmonary embolism	1 (0.2%)	0
Rib fracture	1 (0.2%)	0
Rotator cuff syndrome	1 (0.2%)	0
Sinus node dysfunction	1 (0.2%)	0
Angina pectoris	1 (0.2%)	0
Osteoarthritis	0	2 (0.4%)
Acute myocardial infarction	0	1 (0.2%)
Appendicitis	0	1 (0.2%)
Breast cancer stage II	0	1 (0.2%)
Chest pain	0	1 (0.2%)
Gastric ulcer	0	1 (0.2%)
Hypertension	0	1 (0.2%)
Intervertebral disc degeneration	0	1 (0.2%)
Ischemic stroke	0	1 (0.2%)
Mental status changes	0	1 (0.2%)
Total	10 (2.1%)	10 (2.1%)

Source: Agency generated.

Reviewer comment: All SAEs in subjects treated with HP solution, 40% were single events. The analysis of these SAEs did not suggest a causal relationship. In addition, due to lack of systemic absorption of topically applied HP solution, 40%, it is unlikely that any systemic AE was due to study drug administration.

<u>Phase 2 Trials and Open-label Phase 3 Trial (SEBK-303)</u>
In trial SEBK-201, one subject who received HP solution, 40% experienced one SAE (pyelonephritis acute). No subjects in the vehicle arm experienced an SAE.

In trial SEBK-202, two subjects who received HP solution, 40% experienced two SAEs (atrial fibrillation and laceration) while one subject in the vehicle arm experienced one SAE (breast cancer *in situ*).

In trial SEBK-203, three subjects experienced three SAEs (dizziness, renal failure, and fatal metastatic neoplasm) in the HP 40% arm while one subject in the vehicle arm experienced one SAE (malignant melanoma).

In studies SEBK-205 and SEBK-303, no subject experienced an SAE.

In study RIPT-201, 4 subjects had 4 SAEs (congestive heart failure, rectal bleeding, and hyperglycemia). One subject became pregnant. The event of pregnancy was reported as an SAE and the subject was discontinued from the study. No SAE in study RIPT-201 was considered related to study drug.

No SAE in trial SEBK-201, SEBK-202, SEBK-203, SEBK-205, and SEBK-303 subjects led to discontinuation or was suspected by the investigator of being related to HP solution.

Reviewer comment: Given the lack of systemic absorption of topically applied HP solution, 40%, it is unlikely that systemic AEs were drug related. No local skin reaction was reported as SAE.

The SAE of pregnancy in the healthy subject is discussed in Section 7.6.2.

7.3.3 Dropouts and/or Discontinuations

Table 35: Adverse Events that Led to Drug Withdrawal, HP solution, 40% Development Program

Study	Preferred Term	Serious AE	Intensity	Related to Drug
301	CNS lesion	Yes	Moderate	No
203	Cataract Face injury	No No	Severe Moderate	No
203	Metastatic neoplasm	Yes	Severe	No
101	Dermatitis allergic	No	Mild	Yes
101	Dermatitis	No	Moderate	Yes
101	Pregnancy/Spontaneous abortion	Yes	Severe	No
101	Hyperglycemia	Yes	Severe	No
101	Patella fracture	No	Severe	No

Source: Modified from applicant's submission, Module 2.7.4, ISS, Section 4.2.1.4, Table 11, page 29 and Module 5.3.5.3, A-101-RIPT-101 Clinical Study Report.

Phase 3 Trials (SEBK-301 and SEBK-302)
In trial SEBK-302, no subject discontinued due to AE.
One AE (CNS lesion) in SEBK-301 led to subject discontinuation. This SAE was not considered related to the treatment.

Phase 2 Trials and Open-label Phase 3 Trial (SEBK-303)
In SEBK-203, two subjects experienced 3 AEs that led to study drug discontinuation. One AE (metastatic neoplasm) was an SAE. None these AEs were considered related to treatment.

7.3.4 Significant Adverse Events

No additional significant adverse events were reported during the conduct of studies that support this application.

7.3.5 Submission Specific Primary Safety Concerns

Adverse events of special interest (AESIs) of hair discoloration and LSRs were selected based on the mechanism of action of HP. No cases of hair discoloration were reported during the development program for the SK indication. LSRs are discussed below in common AEs.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Phase 3 Trials (SEBK-301 and SEBK-302)

Local Skin Reactions at Treatment Site
The most frequent AEs reported in Phase 3 trials were LSRs. The applicant actively monitored for the occurrence of LSRs. LSR evaluations were completed by both the investigator (atrophy, crusting, edema, erosion, erythema, hyperpigmentation, hypopigmentation, scaling, scarring, ulceration and vesicles) and subject (pruritus and stinging). Table 36 summarizes the incidence of each LSR. Table 37 provides details of the incidence of LSRs by severity.

Table 36: SEBK-301 and SEBK-302: Percent of Subjects with Local Skin Reactions (Pooled)

	HP 40% N = 467 n (%)	**Vehicle N = 470 n (%)**
Erythema	463 (99%)	159 (34%)
Stinging	454 (97%)	45 (10%)
Edema	425 (91%)	29 (6%)
Scaling	418 (90%)	156 (33%)
Crusting	377 (81%)	88 (19%)
Pruritus	270 (58%)	38 (8%)
Hyperpigmentation	181 (39%)	7 (2%)
Vesicles	114 (24%)	2 (<1%)
Hypopigmentation	90 (19%)	5 (1%)
Erosion	69 (15%)	3 (1%)
Ulceration	40 (9%)	8 (2%)
Atrophy	21 (5%)	0
Scarring	15 (3%)	0

Source: Agency generated.

Table 37. SEBK-301 and SEBK-302: Percent of Subjects with Local Skin Reactions by Severity (Maximum Post-Treatment Rating)

	HP 40% N = 467 n (%)			**Vehicle N = 470 n (%)**		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Subject Reported						
Pruritus	159 (34%)	86 (18%)	25 (5%)	32 (7%)	5 (1%)	1 (<1%)
Stinging	157 (34%)	229 (49%)	68 (15%)	41 (9%)	3 (1%)	1 (<1%)
Investigator Reported						
Atrophy	21 (4%)	0	0	0	0	0
Crusting	159 (34%)	179 (38%)	39 (8%)	61 (13%)	22 (5%)	5 (1%)
Edema	131 (28%)	225 (48%)	69 (15%)	26 (6%)	3 (1%)	0
Erosion	57 (12%)	9 (2%)	3 (1%)	3 (<1%)	0 (0%)	0
Erythema	62 (13%)	313 (67%)	88 (19%)	134 (29%)	24 (5%)	1 (<1%)
Hyperpigmentation	149 (32%)	31 (7%)	1 (<1%)	6 (1%)	1 (<1%)	0
Hypopigmentation	76 (16%)	13 (3%)	1 (<1%)	4 (1%)	1 (<1%)	0
Scaling	229 (49%)	167 (36%)	22 (5%)	130 (28%)	23 (5%)	3 (1%)
Scarring	12 (3%)	2 (<1%)	1 (<1%)	0	0	0
Ulceration	30 (6%)	9 (2%)	1 (<1%)	4 (1%)	4 (1%)	0
Vesicles	97 (21%)	14 (3%)	3 (1%)	2 (<1%)	0	0

Source: Agency generated.

<u>Adverse Reactions Outside of Treatment Site</u>

Adverse reactions occurring outside of treatment sites are presented in table below.

Table 38: SEBK-301 and SEBK-302: Adverse Reactions (Pooled)

	HP 40% N = 467 n (%)	**Vehicle N = 470 n (%)**
Number Subjects with Treatment Related Adverse Events	14 (3%)	1 (0.2%)
Eyelid edema	3 (0.6%)	0
Herpes zoster	3 (0.6%)	1 (0.2%)
Oral herpes	2 (0.4%)	0
Administration/application site pain	2 (0.4%)	0
Angioedema	1 (0.2%)	0
Blepharospasm	1 (0.2%)	0
Burning sensation	1 (0.2%)	0
Eye infection	1 (0.2%)	0
Impetigo	1 (0.2%)	0
Infection	1 (0.2%)	0
Localized infection	1 (0.2%)	0
Lacrimation increased	1 (0.2%)	0
Lip swelling	1 (0.2%)	0
Post procedural complication	1 (0.2%)	0
Procedural headache	1 (0.2%)	0
Pruritus	1 (0.2%)	0
Pruritus generalized	1 (0.2%)	0

Source: Modified from applicant's submission, Module 5.3.5.3, ISS, Table 5.

Reviewer's comment: This reviewer recommends including the incidence and severity of LSR in the labeling for HP solution, 40% due to the high occurrence of LSR reported in the pivotal trials.

Because non-LSR may occur near treatment sites (eyelid edema) or the treatment with an irritant like HP may trigger a recrudescence of latent herpes infection (oral herpes or herpes zoster), this reviewer recommends that AEs of herpes zoster, oral herpes, and eyelid edema be included in labeling.

Phase 2 Trials and Open-label Phase 3 Trial (SEBK-303)

Local Skin Reactions at Treatment Site
Refer to Section 7.5.2 for discussion of these results.

Adverse Reactions Outside of Treatment Site

ARs reported in Phase 2/3 studies are summarized below. Study SEBK-201 was not included because each subject received all three concentrations of HP solution (25%, 32.5% and 40%) as well as vehicle. The safety results of maximal use study (SEBK-205), were not included in the analysis due to different treatment regimen (single application of the study drug) and different study population.

Table 39: Adverse Reactions Outside of Treatment Site for Phase 2 and Open-Label Phase 3 Trials

		HP 40%	HP 32.5%	Vehicle
Study	**Number Subjects with Adverse Reactions**			
SEBK-202 HP 40%: N = 57 HP 32.5%: N = 57 Vehicle: N = 58	Blepharitis	1 (<1%)	0	0
	Dermatitis contact	0	1(<1%)	0
	Pain	0	2 (<1%)	1 (<1%)
	Pain in jaw	0	1 (<1%)	0
	Pain in skin	0	1 (<1%)	0
	Viral infection	0	1 (<1%)	0
SEBL-203 HP 40%: N = 39 HP 32.5%: N = 39 Vehicle: N = 41	Ecchymosis	1 (<1%)	0	0
	Oral herpes	1 (<1%)	0	0
	Face injury	1 (<1%)	0	0
	Skin hemorrhage	0	1 (<1%)	0
SEBK-303 N=147	Dermatitis allergic	1 (<1%)	-	-
	Dermatitis contact	2 (<1%)	-	-
	Herpes zoster disseminated	1 (<1%)	-	-
	Skin irritation	1 (<1%)	-	-

Source: Agency generated.

Reviewer's comment: As discussed above, this reviewer recommends inclusion of herpes zoster and oral herpes in adverse reaction labeling.

7.4.2 Laboratory Findings

Review of laboratory data revealed that mean changes from baseline in hematology and chemistry parameters in both treatment arms were small and not clinically significant.

In the Phase 3 safety population, there were no apparent treatment-related differences in the proportion of subjects with laboratory results outside of the normal range for both hematology and chemistry laboratory studies. No subjects were reported to have hematology laboratory-related treatment emergent AEs (TEAEs). Three subjects had chemistry laboratory-related TEAEs (hypercholesterolemia, hyperkalemia, and hyperlipidemia; 1 subject each); none of which were considered related to study treatment and none were considered severe.

In Phase 2/3 studies, two subjects in SEBK-303 had TEAE of anemia (mild, not related to study drug) and one subject in SEBK-203 had TEAEs of increased glucose and glycosylated hemoglobin (mild, not related to study drug).

Reviewer's comment: Laboratory evaluations (hematology, serum chemistry) revealed that abnormal laboratory values were infrequent, transient and did not lead to study drug discontinuation. No safety signals were revealed.

HP solution, 40% was shown not to be absorbed systemically with topical application. Therefore, laboratory changes due to HP solution, 40% treatment were not expected and this reviewer agrees with the investigator's conclusion that the TEAEs were not clinically significant and not treatment related.

7.4.3 Vital Signs

The mean changes in vital signs during the studies by treatment group were small and not clinically significant.

No subjects in the SEBK-301 and SEBK-302 safety population had vital signs-related TEAEs.

In trial SEBK-303, one subject in HP solution, 40% treatment group experienced TEAE of hypertension. This AE was moderate in severity and deemed by the investigator, not related to study drug.

Reviewer's comment: HP solution, 40% was shown not to be absorbed systemically with topical application. Vital sign changes due to HP 40% are not expected and this reviewer agrees with the investigator's conclusion that the TEAE was not clinically significant.

7.4.4 Electrocardiograms (ECGs)

Study SEBK-201 was the only study in the HP solution, 40% development program to include ECG monitoring. The study enrolled 35 subjects and randomized 4 SKTLs on each subject's back to HP 25%, 32.5%, and 40% solution; and vehicle. ECGs were performed at screening (Visit 1), before treatment randomization (Visit 2) and at end of study (Visit 9). Of 24 subjects, 3 ECGs were reported as abnormal. All three were considered not clinically significant.

Reviewer's comment: HP solution, 40% was shown not to be absorbed systemically with topical application. In reviewing the 3 abnormal ECG results in SEBK-201, this reviewer agrees with the investigator's conclusion that the abnormal ECG were not clinically significant.

The applicant did not conduct a thorough QT/QTc (TQT) study and requested a waiver. The QT-IRT review team agreed that a waiver from requirement to conduct a TQT study for HP solution, 40%, is reasonable.

The QT/IRT review concluded a TQT study was not needed for the following reasons:

- The recommendations in ICH E14 may not apply to products with highly localized distribution and those administered topically and not absorbed.
- HP is an endogenous ubiquitous product of cellular metabolism with endogenous levels in the micromolar range (circulating levels of <1 to 35 μM as per different literature sources).
- No significant changes in basal systemic levels of hydrogen peroxide in blood were observed after A-101 treatment for subjects in the maximal use study A-101- SEBK-205. While there is a possibility that there could be changes in exposure <0.3 μM (LLOD for assay sensitivity), it will not significantly alter the physiological systemic concentration of H2O2 under maximum use conditions.
- The nonclinical data does not suggest potential for hERG inhibition (in fact, supraphysiological concentrations of hydrogen peroxide accelerated the activation of the hERG current resulting in an effective increase in current). A shortening of the cardiac action has been reported in guinea pig myocytes and whole heart. As per the sponsor, these effects were observed at concentrations of 100 μM to 10 mM and considered only reflective of potential local pathophysiological levels attained under conditions of ischemia/reperfusion.
- The dosing for this drug is a single in-office treatment (application by a healthcare professional; not intended for application by patients), so there is no potential for chronic exposure

The reader is referred to the review by Dr. Marathe, MD, for detailed analysis of the TQT study aspects of this application.

Reviewer's comment: In the study SEBK-205, there was no systemic absorption of HP solution, 40% when applied topically under maximal use conditions. Because of the lack of systemic absorption and for the reasons laid out by the TQT team reviewer, it is reasonable not to require conduct of TQT study.

7.4.5 Special Safety Studies/Clinical Trials

Dermal Safety Studies

Phototoxicity and Photoallergenicity

In non-clinical studies, HP was not found not to have the potential for photoirritation or photosensitization, and thus no human phototoxicity or photosensitivity studies were conducted.

Cumulative Irritation

HP is a known skin irritant. This was confirmed during the conduct of Phase 2 and 3 trials, and will be included in labeling.

Sensitization
Study RIPT-101 was conducted to evaluate the sensitization potential of HP solution, 40%. The study enrolled 233 subjects. The applicant reported that the study drug was not sensitizing. However, review of narratives for the 14 dropouts, revealed that two subjects discontinued due to drug related AEs (allergic contact dermatitis and dermatitis).

Reviewer comment: Based on the limited information submitted regarding the cases of allergic contact dermatitis and dermatitis that were deemed study drug related, no clear determination can be made if HP 40% is a potential sensitizer. In addition, no AE of allergic contact dermatitis were reported during the conduct of the Phase 3 trials.

7.4.6 Immunogenicity

This section of the review is not applicable to this product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

During Phase 3 trials, only the 40% concentration was evaluated. In Phase 2 trials, different concentrations of HP solution (25%, 32.5%, and 40%) were evaluated and compared to vehicle.

Reviewer's comment: The AEs in Phase 2 trials were similar in type and incidence to those reported in Phase 3 trials. Due to small sample size in each treatment arm, definite conclusion regarding difference in safety between treatment arms, could not be drawn.

7.5.2 Time Dependency for Adverse Events

Phase 3 Trials (SEBK-301 and SEBK-302)
Subjects in SEBK-301 and SEBK-302 were evaluated for local skin reactions (LSR) prior to treatment at Visit 2 and 4, 10 minutes after treatment at Visit 2 and 4 for subject reported LSR, 20 minutes after treatment at Visit 2 and 4 for investigator graded LSR, 1 week after treatment at Visits 3 and 5, and then at Day 50, 78 and 106. Time dependency of certain LSRs were noted.

Common local skin reactions observed 10 – 20 minutes after treatment include: erythema (98%), stinging (93%), edema (85%), pruritus (32%), and vesiculation (18%).

Common local skin reactions observed 1 week after treatment are scaling (72%), crusting (67%), erosion (9%), and ulceration (4%).

The table below summarize the incidence of LSR in subjects with at least one SKTL with an LSR severity score greater than "none."

Table 40: SEBK-301 and SEBK-302 (Pooled): Local Skin Reactions by Maximal Occurrence by Visit

Local Skin Reaction	Greatest Incidence Reported				Visit of Greatest Incidence
	HP 40% N=470		Vehicle N=467		
10 Minutes after Treatment	n	%	n	%	
Subject Reported					
Stinging	434	**93%**	30	6%	2/after med
Pruritus	147	**33%**	7	2%	2/after med
20 minutes after Treatment					
Investigator Reported					
Erythema	446	**98%**	89	19%	4/after med
Edema	387	**85%**	15	3%	4/after med
Vesicles	86	**18%**	2	<0.5%	2/after med
One Week after Treatment					
Scaling	335	**72%**	81	17%	3
Crusting	312	**67%**	46	10%	3
Erosion	39	**9%**	0	0	5
Ulceration	20	**4%**	3	1%	5
End of Study (Day 106)					
Hyperpigmentation	84	**18%**	3	1%	8
Hypopigmentation	32	**7%**	1	<0.5%	8
Atrophy	8	**3%**	0	0	7
Scarring	5	**1%**	0	0	8

Source: Modified from applicant's submission, Module 5.3.5.3, Table 11.
Visit 2 considered baseline visit. N = subjects completing study. Each grade pooled across all lesions to calculate percentage per visit.

The table below summarizes the LSRs occurring in at least 1% of subjects at the end of study visit/Day 106.

Table 41: SEBK-301 and SEBK-302 (Pooled): Local Skin Reactions Occurring in ≥1% of Subjects at the End of Study Visit.

	HP 40% N=470	**Vehicle N=467**
	n (%)	**n (%)**
Erythema	98 (21%)	10 (2%)
Hyperpigmentation	84 (18%)	3 (1%)
Crusting	54 (12%)	34 (7%)
Hypopigmentation	32 (7%)	1 (<1%)
Scarring	5 (1%)	0
Atrophy	3 (1%)	0
Scaling	72 (16%)	51 (11%)
Pruritus	9 (2%)	7 (2%)

Source: Modified from applicant's submission, Module 5.3.5.3, Table 11.
Visit 2 considered baseline visit. N = subjects completing study. Each grade pooled across all lesions to calculate percentage per visit.

Discussion: As a known irritant, active surveillance for LSRs was conducted. Subjects treated with HP solution, 40% had greater rates of local skin reactions compared to subjects receiving vehicle. Of note, the occurrence of the LSRs differed with time, with some peaking immediately after treatment (stinging, pruritus, and edema); some peaking one week after treatment (scaling, erosion, crusting, ulceration, and vesicles) and; some peaking towards the end of the trial (atrophy, discoloration, scarring).

The time dependency of certain LSRs relative to treatment is reasonable given the natural course of wound healing. Because local skin reactions of atrophy, discoloration and scarring can have high impact when localized in esthetically sensitive areas (face), this reviewer that the ARs of LSRs be communicated in labeling.

Phase 2 Trials and Open-Label Phase 3 Trial (SEBK-303)

In Phase 2/3 trials, LSRs were the most commonly reported AEs. The tables below summarize the incidence of LSR in subjects with at least 1 SKTL with an LSR severity score greater than "none" by visit occurrence.

Table 42: SEBK-201: Local Skin Reactions by Maximal Occurence by Visit

Local Skin Reaction	Greatest Incidence Reported								Visit of Greatest Incidence
	HP 40% N=34		HP 32.5% N=34		HP 35% N=34		Vehicle N=34		
	n	%	n	%	n	%	n	%	
Subject Reported									
10 Minutes after Treatment									
Pruritus	8	**24%**	11	32%	8	24%	0	0	2/after med
One week after Treatment									
Stinging	25	**79%**	23	71%	21	65%	8	24%	5/after med
Investigator Reported									
20 Minutes after Treatment									
Induration	34	**100%**	34	100%	34	100%	34	100%	2 before and after med
Erythema	34	**100%**	34	100%	33	97%	6	18%	5/after med
Edema	33	**97%**	30	88%	21	65%	0	0	5/after med
One Week after Treatment									
Crusting	21	**62%**	19	56%	11	32%	3	9%	6
Scaling	7	**23%**	5	15%	1	3%	0	0	6
Erosion	1	**3%**	0	0	0	0	0	0	6
Hypopigmentation	1	**3%**	0	0	2	6%	0	0	6
Visit 8 (Day 57) and End of Study (Day 78)									
Atrophy	1	**31%**	0	0	0	0	0	0	8 and 9
Hyperpigmentation	3	**9%**	2	6%	1	3%	0	0	8
No Reports for HP 40%									
Ulceration	0	**0**	0	0	0	0	0	0	-
Vesicles	0	**0**	0	0	0	0	0	0	-
Keloid Scarring	0	**0**	0	0	0	0	0	0	-

Source: Modified from applicant's submission, Module 5.3.5.1, CSR 201, Table 9.7.1 and 9.7.2.

Table 43: SEBK-202: Local Skin Reaction by Maximal Occurrence by Visit

Local Skin Reaction	Greatest Incidence Reported						Visit of Greatest Incidence
	HP 40% N=57		HP 32.5% N=57		Vehicle N=58		
	n	%	n	%	n	%	
10 Minutes after Treatment – Subject Reported							
Stinging	49	**88%**	43	77%	4	7%	2/after med
Pruritus	17	**30%**	19	34%	2	4%	2/after med
Investigator Reported							
20 Minutes after Treatment							
Erythema	56	**100%**	56	100%	31	54%	2/after med
Edema	54	**96%**	54	96%	11	29%	2/after med
Vesicles	4	**7%**	2	4%	0	0%	4/after med
One Week after Treatment							
Crusting	55	**98%**	49	88%	17	30%	5
Scaling	35	**63%**	27	48%	7	12%	5
Erosion	7	**13%**	6	11%	0	0%	5
Ulceration	1	**2%**	0	0%	0	0%	5
Visit 7 or End of Study (Day 106)							
Hyperpigmentation	17	**30%**	8	14%	0	0%	7
Hypopigmentation	2	**4%**	2	4%	2	4%	8
Scarring	2	**4%**	3	5%	0	0	8
Atrophy	1	**2%**	0	0%	0	0%	8

Source: Modified from applicant's submission, Module 5.3.5.1, CSR 202, Table 9.7.3 and 9.7.4.

Table 44: SEBK-203: Local Skin Reaction by Maximal Occurrence by Visit

Local Skin Reaction	Greatest Incidence Reported						Visit of Greatest Incidence
	HP 40% N=39		HP 32.5% N=39		Vehicle N=40		
	n	%	n	%	n	%	
10 Minutes after Treatment – Subject Reported							
Stinging	37	**95%**	28	72%	3	7%	2/after med
Pruritus	7	**24%**	6	21%	1	3%	4/after med
Investigator Reported							
20 minutes after Treatment							
Erythema	37	**95%**	38	97%	39	16%	2/after med
Edema	36	**92%**	30	77%	4	10%	2/after med
One Week after Treatment							
Crusting	26	**68%**	19	49%	4	10%	3
Scaling	19	**50%**	16	41%	1	2%	3
Erosion	2	**5%**	2	5%	0	0	3
Atrophy	1	**3%**	0	0	0	0	5
Three Weeks after Treatment							
Hyperpigmentation	3	**8%**	0	0	0	0	4/prior to med
Visit 7 or End of Study (Day 106)							
Hypopigmentation	1	**3%**	0	0	0	0	7
No Reports for HP 40%							
Scarring	0	**0**	0	0	0	0	-
Ulceration	0	**0**	0	0	0	0	-
Vesicles	0	**0**	0	0	0	0	-

Source: Modified from applicant's submission, Module 5.3.5.1, CSR 203, Table 9.7.3 and 9.7.4.

Table 45: SEBK-303: Local Skin Reactions by Maximal Occurrence by Visit

Local Skin Reaction	Greatest Incidence Reported		Visit of Greatest Incidence
	HP 40% N=147		
	n	%	
10 Minutes after Treatment – Subject Reported			
Stinging	119	**81%**	2/after med
Pruritus	52	**35%**	2/after med
Investigator Reported 20 minutes after Treatment			
Erythema	135	**96%**	6/after med
Scaling	108	**74%**	2/after med
Edema	77	**57%**	8/after med
Vesicles	16	**11%**	4/after med
One Week after Treatment			
Crusting	76	**52%**	3
Atrophy	11	**8%**	6/before med and 7
Erosion	7	**5%**	7
Scarring	5	**4%**	9
Ulceration	2	**1%**	3 and 5
Three Weeks after Treatment			
Hyperpigmentation	35	**25%**	12
End of Study (Day 148)			
Hypopigmentation	20	**15%**	12

Source: Modified from applicant's submission, Module 5.3.5.2, CSR 303, Table 14.3.5.3 and 14.5.5.4.

Reviewer's comment: The Phase 2 studies, open-label Phase 3 study and vehicle-controlled Phase 3 pivotal trials have a similar pattern of LSR incidence and time course of occurrence.

7.5.3 Drug-Demographic Interactions

In the safety population, most subjects were white and neither Hispanic or Latino. The difference in sample size between White and Non-White subjects; and Hispanic or Latino and neither Hispanic or Latino subjects prevented drawing meaningful conclusion regarding effect of drug treatment by race and ethnicity.

Analysis of effects of drug treatment by gender and age did not reveal a consistent pattern of higher incidence of AEs in these subgroups. LSR were reported at a high enough incidence to make comparisons, while the reporting of other AEs occurred in such small numbers that no conclusions could be made. The results are summarized in tables below.

Age
The applicant did not include LSR as AEs, and thus we analyzed LSR separately from AEs for any differences due to age. Due to the small number of reported AEs, no definitive conclusions regarding the age and occurrence of AEs, could be drawn.

Table 46: Local Skin Reactions by Age Group for HP 40% Treatment Arm (Pooled)

LSR	Age Group		
	18 – 55	56 – 70	71+
	HP 40%	HP 40%	HP 40%
	N=34 n (%)	N=244 n (%)	N=189 n (%)
Atrophy	1 (3%)	**11 (5%)**	**9 (5%)**
Crusting	30 (88%)	189 (78%)	158 (84%)
Edema	31 (91%)	223 (91%)	171 (91%)
Erosion	6 (18%)	38 (16%)	25 (13%)
Erythema	34 (100%)	243 (100%)	186 (99%)
Hyperpigmentation	13 (38%)	102 (42%)	66 (35%)
Hypopigmentation	7 (21%)	50 (21%)	33 (18%)
Pruritus	22 (65%)	138 (57%)	110 (58%)
Scaling	31 (91%)	221 (91%)	166 (88%)
Scarring	0	**9 (4%)**	**6 (3%)**
Stinging	33 (97%)	239 (98%)	182 (96%)
Ulceration	**5 (15%)**	18 (7%)	17 (9%)
Vesicles	6 (18%)	61 (25%)	47 (25%)

Source: Agency generated.

Reviewer's comment: Subjects older than 55 have a higher incidence of atrophy and scarring compared to subjects age 18 – 55 years-old (5% versus 3% and 3-4% versus 0%, respectively) that may be due to age related skin changes. Subjects 18-55 years-old have a higher incidence of ulceration (15%) compared to subjects older than 55 years-old (7-8%) that may be related to older individuals have thicker SKs.

Table 47: Adverse Events by Age Groups (Pooled)

	Pooled 18-55		**Pooled 56-70**		**Pooled 71+**	
	HP 40% N = 34 n (%)	**Vehicle N = 30 n (%)**	**HP 40% N = 244 n (%)**	**Vehicle N = 238 n (%)**	**HP 40% N = 189 n (%)**	**Vehicle N = 202 n (%)**
# of AEs reported	22	4	52	56	71	66
# of Subjects with AEs	15 (44.1%)	4 (13.3%)	39 (16.0%)	42 (17.6%)	46 (24.3%)	42 (20.8%)
# of SAEs reported	3	0	0	4	11	7
# of Subjects with SAE	2 (5.9%)	0	0	4 (1.7%)	8 (4.2%)	6 (3.0%)
Subjects with AE by Severity						
Missing	0	0	0	0	0	0
Mild	7 (20.6%)	1 (3.3%)	17 (7.0%)	22 (9.2%)	14 (7.4%)	13 (6.4%)
Moderate	5 (14.7%)	2 (6.7%)	21 (8.6%)	17 (7.1%)	23 (12.2%)	21 (10.4%)
Severe	3 (8.9%)	1 (3.3%)	1 (0.4%)	3 (1.3%)	9 (4.8%)	8 (4.0%)
Subjects with SAE by Severity						
Missing	0	0	0	0	0	0
Mild	0	0	0	1 (0.4%)	0	0
Moderate	0	0	0	0	3 (1.6%)	1 (0.5%)
Severe	2 (5.9%)	0	0	3 (1.3%)	5 (2.6%)	5 (3.0%)

Source: Agency generated.

Sex

The applicant did not include LSR as AEs, and thus we analyzed LSR separately from AEs for any differences due to sex. The LSRs occur in similar rates across gender except for scarring where 13/286 (4.6%) women compared to 2/181 (1.1%) men reported scarring. Due to the small number of reported AEs, no meaningful conclusions could be drawn in regards to sex.

Table 48: Local Skin Reactions by Sex for HP 40% Treatment Arm (Pooled)

LSR	Women N=286 n (%)	Men N=181 n (%)
Atrophy	12 (4%)	9 (5%)
Crusting	222 (78%)	155 (86%)
Edema	253 (89%)	172 (95%)
Erosion	39 (14%)	30 (17%)
Erythema	283 (99%)	180 (100%)
Hyperpigmentation	106 (37%)	75 (41%)
Hypopigmentation	54 (19%)	36 (20%)
Pruritus	169 (59%)	101 (56%)
Scaling	254 (89%)	164 (91%)
Scarring	13 (5%)	2 (1%)
Stinging	276 (97%)	178 (98%)
Ulceration	28 (10%)	12 (7%)
Vesicles	70 (25%)	44 (24%)

Source: Agency generated

Table 49: Adverse Events by Sex (Pooled)

	Pooled		Pooled Women		Pooled Men	
	HP 40% N = 467 n (%)	Vehicle N = 470 n (%)	HP 40% N = 286 n (%)	Vehicle N = 262 n (%)	HP 40% N = 181 n (%)	Vehicle N = 208 n (%)
# of AEs reported	145	126	86	69	59	57
# of Subjects with AEs	100 (21%)	88 (19%)	64 (22%)	50 (19%)	36 (20%)	38 (18%)
# of SAEs reported	14	11	5	5	9	6
# of Subjects with SAE	10 (2%)	10 (2%)	3 (1%)	5 (2%)	7 (4%)	5 (2%)
Subjects with AE by Severity						
Missing	0	0	0	0	0	0
Mild	38 (8%)	36 (8%)	21 (7%)	25 (10%)	17 (9%)	11 (5%)
Moderate	49 (11%)	40 (9%)	36 (13%)	19 (7%)	13 (7%)	21 (10%)
Severe	13 (3%)	12 (3%)	7 (2%)	6 (2%)	6 (3%)	6 (3%)
Subjects with SAE by Severity						
Missing	0	0	0	0	0	0
Mild	0	1 (<1%)	0	1 (<1%)	0	0
Moderate	3 (1%)	1 (<1%)	1 (<1%)	1 (<1%)	2 (1%)	0
Severe	7 (2%)	8 (2%)	2 (1%)	3 (1%)	5 (3%)	5 (2%)

Source: Modified from applicant's submission, Module 5.3.5.3, ISS, Table 4, 4.1, and 4.1.1 and Module 2.7.4, ISS, Section 4.5.1.1, Table 12, page 35.

Race
In the two Phase 3 trials, 98% were White, < 0.05% were Black, <0.05% were Asian, and the remainder were of other races (less than 0.01% each). Due to the small number of subjects of non-White race, no meaningful conclusions could be drawn with regard to AEs and LSR, and race.

Ethnicity
In the two Phase 3 trials, 4% of subjects were Hispanic or Latino and 95% were neither Hispanic or Latino. Due to the small number of Hispanic or Latino subjects, no meaningful conclusions could be drawn regarding AEs and LSR, and ethnicity.

Region
All studies were conducted in the United States.

7.5.4 Drug-Disease Interactions

Given the rapid degration of HP with contact on skin and its lack of systemic absorption with topical application shown in SEBK-205, HP solution, 40% is not suspected of having any drug-disease interactions.

7.5.5 Drug-Drug Interactions

The potential for drug-drug interactions was evaluated in both the clinical pharmacology and Phase 2 studies. Given the lack of systemic absorption with topical application of HP solution, 40% shown in SEBK-205, no drug-drug interactions were suspected or evaluated for during Phase 3 trials.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Malignancies (skin and solid tumors) were reported during the development program of HP solution, 40%. However, given the time points at which malignancies were reported (not reflective of the generally long latency periods for development of malignancies or with treatment sites) and the types of malignancies reported, it is the reviewer's opinion that it is unlikely that the study drug was a causative agent. No pattern to the type of malignancies was observed.

7.6.2 Human Reproduction and Pregnancy Data

During the development program for the SK indication, one healthy subject in the RIPT study, RIPT-101, reported a pregnancy. She had a history of 3 spontaneous abortions,

and was discontinued at Visit 11/Day21 due to pregnancy. She subsequently had a spontaneous abortion which was reported as an SAE.

Topical use of HP solution, 40% under maximal use was shown in study SEBK-205 to not increase endogenous serum levels of HP. Thus, maternal use is not expected to result in fetal exposure to elevated physiologic levels of HP or lead to an increase in physiologic levels of HP in breast milk.

7.6.3 Pediatrics and Assessment of Effects on Growth

All trials supporting this application were conducted in adult subjects (18 years of age and older), for the population for whom the applicant seeks approval.

The applicant submitted a request for a waiver for pediatric patients 0 to less than 18 years of age. The reason stated for waiving studies in the pediatric age group is that *studies would be impossible or highly impracticable* given the rarity of SKs in the pediatric population. The Agency agreed with applicant's request and granted the full waiver from conducting studies in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Based on the mode of action and dosing regimen, there is no reason to assume that there is a potential for abuse or dependency of HP solution, 40%.

7.7 Additional Submissions / Safety Issues

There are no additional submissions or safety issues for this drug product for this indication in this population.

8 Postmarket Experience

There has been no postmarket experience for this product at the time of this review.

9 Appendices

9.1 Literature Review/References

1. Jackson JM, Alexis A, Berman B, et al. Current understanding of seborrheic keratosis: prevalence, etiology, clinical presentation, diagnosis, and management. J Drugs Dermatol 2015;14(10):1119-1125.
2. Yeatman JM, Kilkenny M, Marks R. The prevalence of seborrheic keratoses in Australian population: does exposure to sunlight play a part in their frequency? Br J Dermatol 1997;137:411-414.

9.2 Labeling Recommendations

Labeling recommendations are ongoing at the time of this review.

9.3 Advisory Committee Meeting

No Advisory Committee meeting was held for this drug development program.

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/s/

MELISSA A REYES
11/21/2017

SNEZANA TRAJKOVIC
11/21/2017