CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Applicant:	Aclaris
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1 Executive Summary

Hydrogen peroxide solution, 40% was superior to vehicle solution in the treatment of seborrheic keratoses (SK). Studies 301 and 302 enrolled subjects age 18 and older with stable clinically typical SK including 4 SK target lesions on the trunk, extremities, and face suitable for treatment. At least 1 target lesion was to be on the trunk or extremities and at least 1 target lesion was to be on the face. Each target lesion was to be discrete, with length 5-15 mm, width 5-15 mm, and thickness ≤ 2 mm. At baseline target lesions were to have Physician's Lesion Assessment of 'Thin: a visible SK lesion (thickness ≤ 1 mm)' or 'Thick: a visible SK lesion (thickness > 1 mm)'. Efficacy was demonstrated on the primary endpoint of complete clearance of all target lesions at Day 106 and the secondary endpoint of at least 3 out of 4 target lesions achieving complete clearance at Day 106 in both studies. See Table 1.

Table 1 - Primary and Secondary Endpoints at Day 106 (ITT, Non-Responder Imputation)

	Study 301			Study 302		
	Hyd. Per. N=223	Vehicle N=227	P-value	Hyd. Per. N=244	Vehicle N=243	P-value
All 4 lesions clear	9 (4.0%)	0 (0%)	0.002	19 (7.8%)	0 (0%)	<0.001
≥ 3 lesions clear	30 (13.5%)	0 (0%)	<0.001	56 (23.0%)	0 (0%)	<0.001

The proportion of subjects with missing data was small (<2%) and the results were not impacted by the handling of missing data. In Study 302, the response rate on the hydrogen peroxide arm was nearly twice the response rate observed in Study 301. The higher response rate in Study 302 was driven by the results at a single center, as this center enrolled about 9% of the total subjects, but includes 53% of the subjects who achieved complete clearance. However, if the center with the high proportion of responders is removed from the analysis, the response rate from the remaining centers is similar to the response rate observed in Study 301 (4%). In a sensitivity analyses where the center with the high proportion of responders is removed, the results of Study 302 remain statistically significant.

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

Local skin reactions were common with stinging, pruritus, vesicles, edema, and erythema all peaking after each treatment and then subsiding over time.

2 Introduction

2.1 Overview

2.1.1 Clinical Studies

Hydrogen peroxide (HP) topical solution, 40% is being developed for the treatment of seborrheic keratoses (SK). The applicant conducted three Phase 2 dose-ranging studies (Studies 201, 202, and 203) and two Phase 3 trials (Studies 301 and 302) in subjects with seborrheic keratoses. All five studies were conducted in the U.S. The Phase 3 trials were identical in design and were randomized, double-blind, vehicle-controlled, parallel group trials. See Table 2 for an overview of the clinical trial designs. Additional details for the Phase 3 studies are provided in Table 3. This review will focus on the two Phase 3 trials.

Table 2 – Clinical Trials Overview

Study	**201**	**202**	**203**	**301**	**302**
Design	Within-Subject	Parallel Group	Parallel Group	Parallel Group	Parallel Group
Treatment arms and Sample Size	HP 40%, HP 32.5%, HP 25%, Veh. / 35	HP 40% / 57 HP 32.5% / 57 Veh. / 58	HP 40% / 41 HP 32.5% / 39 Veh. / 39	HP 40% / 223 Vehicle / 227	HP 40% / 244 Vehicle / 243
Treatment area	4 lesions on the back	4 lesions on the extremities or trunk	4 lesions on the face	4 lesions (at least 1 face, 1 extremities or trunk)	4 lesions (at least 1 face, 1 extremities or trunk)
Primary endpoint	Change in PLA at Day 78	Mean percent of clear lesions at Day 106	Mean change in PLA at Day 106	Subjects with all lesions cleared at Day 106	Subjects with all lesions cleared at Day 106

PLA = Physician's Lesion Assessment (4-point scale for assessing individual lesions with categories of clear, near clear, thin, and thick)

Table 3 – Phase 3 Clinical Trials

Study Numbers	301 and 302
Inclusion criteria	Age 18 and older with 4 clinically typical seborrheic keratosis lesions on the trunk, extremities, and face. Each target lesion was to have PLA ≥ 2 (thin or thick), with length and width 5-15 mm, and ≤ 2 mm thickness
Treatment regimen	Target lesions treated at Day 1 and Day 22 (for any lesions with PLA > 0)
Follow-up	15 weeks (Day 106)
Primary endpoint	Subjects with all 4 lesions cleared at Day 106
Secondary endpoint	Subjects with at least 3 out of 4 lesions cleared at Day 106
Study location	US
Study dates	Study 301: Feb. 2016 – Nov. 2016 Study 302: Jan. 2016 – Oct. 2016

2.1.2 Regulatory History

A Pre-IND meeting was held on 4/24/2013. IND 117635 was opened on 9/16/2013 with the protocol for Study 201. Three additional meetings were held with the applicant during the development program: a Guidance Meeting (2/25/2015), an End-of-Phase 2 Meeting (5/6/2015), and a Pre-NDA meeting (9/28/2016). In addition, a Guidance Meeting was scheduled for 12/16/2015 but was canceled by the applicant after receiving the pre-meeting communication.

At the End-of-Phase 2 meeting, the applicant and Agency reached agreement that the studies would enroll subjects with a minimum of 4 lesions on the face, trunk, and extremities, and that the primary endpoint would be defined as complete clearance of all 4 target SK lesions. The Phase 3 protocols (Protocols 301 and 302) were submitted to the IND on 6/22/2015. The study designs were consistent with the agreements reached at the End-of-Phase 2 Meeting and the statistical reviewer provided comments on the role of proposed 'ancillary' analyses, handling of missing data, and the definition of the per protocol population.

2.2 Data Sources

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted. The analysis datasets used in this review are archived at \\cdsesub1\evsprod\nda209305\0001\m5\datasets\.

3 Statistical Evaluation

3.1 Data and Analysis Quality

The databases for the studies required minimal data management prior to performing analyses. The primary and secondary efficacy endpoints needed to be derived by the reviewer from the PLA scores recorded in the datasets, as they were not already derived in the datasets. No information requests regarding datasets or analyses were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Statistical Analysis

Studies 301 and 302 were randomized, double-blind trials evaluating hydrogen peroxide topical solution, 40% versus vehicle in the treatment of seborrheic keratoses. The trials enrolled subjects age 18 and older with a diagnosis of stable clinically typical SK and 4 appropriate SK target lesions on the trunk, extremities, and face. At least 1 target lesion was to be on the trunk or extremities and at least 1 target lesion was to be on the face. Each target lesion was to be discrete, with length 5-15 mm, width 5-15 mm, and thickness $\leq$ 2 mm. Lesions were evaluated on the Physician's Lesion Assessment (PLA) defined below. At baseline target lesions were to have PLA $\geq$ 2.

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

Study treatment was applied by the investigator at baseline. Investigators applied solution to each target lesion for approximately 20 seconds. After 60 seconds the application cycle was repeated. Each lesion was to be treated 4 times. Target lesions with PLA > 0 at Day 22 were to be retreated. Subjects were evaluated as screening, baseline (Day 1), and Days 8, 22, 29, 50, 78, and 106. Efficacy was assessed at Day 106.

Study 301 enrolled 450 subjects (223 on HP and 227 on vehicle) at 17 centers in the US. Study 302 enrolled 487 subjects (244 on HP and 243 on vehicle) at 17 centers in the US. Complete blocks of size 4 (randomized 1:1) were allocated to each center and dispensed in numerical order.

Efficacy was assessed using the PLA scale and length and width measurements. The primary efficacy endpoint was the proportion of subjects with all 4 target lesions cleared (PLA=0) at Day 106. The secondary efficacy endpoint was the proportion of subjects with at least 3 out of 4 target lesions cleared (PLA=0) at Day 106. Following the protocol, complete response and partial response were analyzed with the Cochran-Mantel-Haenszel test stratified by center. Homogeneity was assessed using the Breslow-Day test. Subjects with missing PLA scores at Day 106 were imputed as non-responders. Analyses based on the per protocol population were supportive. In addition, a sensitivity analysis for handling missing data using multiple imputation was conducted. For the multiple imputation, missing PLA data was imputed using monotone logistic option in PROC MI in SAS. Fifty datasets were imputed and the model included terms for baseline PLA and center. The CMH general association statistic from each imputation was transformed using the Wilson-Hilferty transformation.

The ITT population was defined as all randomized subjects. The per protocol population was comprised of subjects who met the inclusion and exclusion criteria, did not use prohibited therapies, had all required study medication treatments, and completed the Day 106 visit with a window of ± 14 days.

3.2.2 Subject Disposition

Study 301 enrolled 450 subjects (223 on HP and 227 on vehicle) and Study 302 enrolled 487 subjects (244 on HP and 243 on vehicle). Approximately 1% of subjects discontinued from Study 301 and 2% discontinued from Study 302. The most common reasons for study discontinuation were withdrawal of consent and lost to follow-up. See Table 4.

Table 4 – Disposition of Subjects in Studies 301 and 302

	Study 301		Study 302	
	HP	Vehicle	HP	Vehicle
Subjects Randomized	223	227	244	243
Discontinued	3 (1.3%)	1 (0.4%)	0	8 (3.3%)
Adverse event	1 (0.4%)	1 (0.4%)	--	--
Subject withdrew consent	2 (0.9%)	--	--	2 (0.8%)
Lost to follow-up	--	--	--	5 (2.1%)
Other	--	--	--	1 (0.4%)

Source: pg 37 of Study A-101-SEBK-301 Study Report Body and pg 37 of Study A-101-SEBK-302 Study Report Body

3.2.3 Baseline Characteristics

Baseline demographics were generally balanced across the treatment groups in the two studies. The mean age was 69 years in both studies. Approximately 42% of subjects were at least 71 years of age, 58% were female, 98% were white, and 2-5% were Hispanic or Latino. See Table 5.

Table 5 – Demographics in Studies 301 and 302

	Study 301		Study 302	
	HP N=223	Vehicle N=227	HP 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 Afric.-Amer.	1 (0.4%)	1 (0.4%)	3 (1%)	3 (1%)
Am. Ind./ AK Native	--	--	--	1 (0.4%)
Asian	2 (0.9%)	4 (2%)	--	2 (0.8%)
Native HI/ Pac. Isl.	--	--	--	--
Other	1 (0.4%)	1 (0.4%)	--	1 (0.4%)
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: pg 38 of Study A-101-SEBK-301 Study Report Body and pg 39 of Study A-101-SEBK-302 Study Report Body

All 4 target lesions were to have baseline PLA score of 2 or 3. The mean baseline PLA score was 2.3. In Study 301, approximately 48% of subjects had all 4 lesions with baseline PLA of 2, while in Study 302, approximately 33% of subjects had all 4 lesions with baseline PLA of 2. A small proportion of subjects had all target lesions with baseline PLA of 3 with the remainder having a mixture of lesions with PLA 2 and 3. Baseline PLA scores were balanced across treatment arms in the two studies. The average total lesion area (sum of 4 target lesions longest length x longest perpendicular) was about 242 mm^2 in Study 301 and 254 mm^2 in Study 302. Total lesion area was balanced across the treatment arms in the two studies. All subjects were to have at least 1 lesion on the face and 1 lesion on the trunk or extremities. The majority of subjects had one lesion on the face. The distribution of the number of facial lesions was balanced across the treatment arms. See Table 6.

Table 6 – Baseline Disease Characteristics

	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
Number on Face				
1	188 (84%)	182 (80%)	197 (81%)	210 (86%)
2	27 (12%)	38 (17%)	33 (14%)	25 (10%)
3	8 (4%)	7 (3%)	14 (6%)	8 (3%)

[a] Sum of 4 target lesions longest length x longest perpendicular
Source: 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.

3.2.4 Efficacy Endpoints

Hydrogen peroxide solution was superior to vehicle solution in both studies on the primary efficacy endpoint of achieving clearance on all 4 target lesions at Day 106 and the secondary endpoint of at least 3 lesions cleared at Day 106. Response rates were analyzed using the Cochran-Mantel-Haenszel test stratified on center. Subjects with missing data were imputed as non-responders. See Table 7.

Table 7 - Primary and Secondary Endpoints at Day 106 (ITT, Non-Responder Imputation)

	Study 301			Study 302		
	Hyd. Per. N=223	Vehicle N=227	P-value	Hyd. Per. N=244	Vehicle N=243	P-value
All 4 lesions clear	9 (4.0%)	0 (0%)	0.002	19 (7.8%)	0 (0%)	<0.001
≥ 3 lesions clear	30 (13.5%)	0 (0%)	<0.001	56 (23.0%)	0 (0%)	<0.001

Source: pg 40 of Study A-101-SEBK-301 Study Report Body and pg 40-41 of Study A-101-SEBK-302 Study Report Body

The protocol specified that the homogeneity across centers would be assessed using the Breslow-Day test; however, because there were no responders on the vehicle arm in either study, the Breslow-Day statistic could not be calculated. See Section 3.2.5 for additional discussion of by-center results.

The protocol stated that two supportive analyses would be conducted: a sensitivity analyses handling missing data using multiple imputation and a per protocol analysis. Because of the limited amount of missing data and the 0% response rate on the vehicle arm, the multiple imputation analysis and the per protocol analysis results were very similar to the primary analysis using non-responder imputation. See Table 8.

Table 8 – 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 (4.1%)	0/221 (0%)	0.002	19/233 (8.2%)	0/236 (0%)	<0.001
Multiple Imputation	9/223 (4.0%)	0/227 (0%)	0.002	19/244 (7.8%)	0/243 (0%)	<0.001

Source: pg 40 of Study A-101-SEBK-301 Study Report Body and pg 40 of Study A-101-SEBK-302 Study Report Body

Relatively few subjects in Studies 301 and 302 achieved clearance on all 4 target lesions. Table 9 presents the number of subjects with 0, 1, 2, 3, and 4 lesions cleared at Day 106. Approximately 42% of hydrogen peroxide subjects in Study 301 and 37% of hydrogen peroxide subjects in Study 302 had no lesions clear compared 94-95% of vehicle subjects. The hydrogen peroxide subjects had mean of 1 to 1.4 lesion clear compared to a mean of 0.02 to 0.07 lesions clear on the vehicle arm.

Table 9 - Number of Cleared Lesions at Day 106 (Subject Level)

	Study 301		Study 302	
	Hyd. Per. N=223	Vehicle N=227	Hyd. Per. N=244	Vehicle N=243
4	9 (4.0%)	0 (0%)	19 (7.8%)	0 (0%)
3	21 (9.4%)	0 (0%)	37 (15.2%)	0 (0%)
2	29 (13.0%)	4 (1.8%)	47 (19.3%)	1 (0.4%)
1	68 (30.5%)	9 (4.0%)	51 (20.9%)	4 (1.6%)
0	93 (41.7%)	213 (93.8%)	90 (36.9%)	231 (95.1%)
Missing	3 (1.3%)	1 (0.4%)	0 (0%)	7 (2.9%)
Mean (LOCF)	1.0	0.07	1.4	0.02

Source: Reviewer analysis.

Complete clearance rates were similar for subjects who had 4 thin lesions (PLA=2) versus those subjects who had at least one thick lesion (PLA=3). Complete clearance rates were also similar for subjects whose total lesion area was less than the median and for subjects whose total lesion area was greater than the median. Complete clearance rates were higher for subjects who had more than one lesion on the face. See Table 10. However, as the overall response rate is very small, it would be difficult to detect a differential treatment effect by baseline disease characteristics. See also the lesion level analyses in Section 3.2.6.

Table 10 – Complete Clearance Rate by Baseline Disease Characteristics

	Study 301		Study 302	
	HP N=223	Vehicle N=227	HP N=244	Vehicle N=243
Baseline PLA				
All PLA = 2	5/107 (4.7%)	0/111 (0%)	7/82 (8.5%)	0/81 (0%)
At least one PLA = 3	4/116 (3.4%)	0/116 (0%)	12/162 (7.4%)	0/162 (0%)
Total Lesion Area				
≤ Median[a]	4/104 (3.9%)	0/124 (0%)	10/117 (8.6%)	0/128 (0%)
> Median	5/119 (4.2%)	0/103 (0%)	9/127 (7.1%)	0/115 (0%)
Number on Face				
1	7/188 (3.7%)	0/182 (0%)	9/197 (4.6%)	0/210 (0%)
2	2/27 (7.4%)	0/38 (0%)	6/33 (18.2%)	0/25 (0%)
3	0/8 (0%)	0/7 (0%)	4/14 (28.6%)	0/8 (0%)

[a] Baseline median of the total lesion area per subject across both treatment arms was 225 mm^2 in Study 301 and 247 mm^2 in Study 302.
Source: 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

The majority of subjects had at least 3 lesions retreated at Day 22, though a few subjects had 2 or fewer lesions retreated. In Study 301, only one subject had all 4 lesions with PLA = 0 at Day 22 that did not need retreatment. By Day 106 only 2 of the 4 lesions

remained cleared, so this subject did not achieve complete clearance at Day 106. In Study 302, 6 subjects had all 4 lesions with PLA =0 at Day 22 that did not need retreatment. All 6 subjects in Study 302 that did not need a second treatment maintained complete clearance at Day 106 and were responders. See Table 11.

Table 11 – Complete Clearance Rate by Number of Treatments

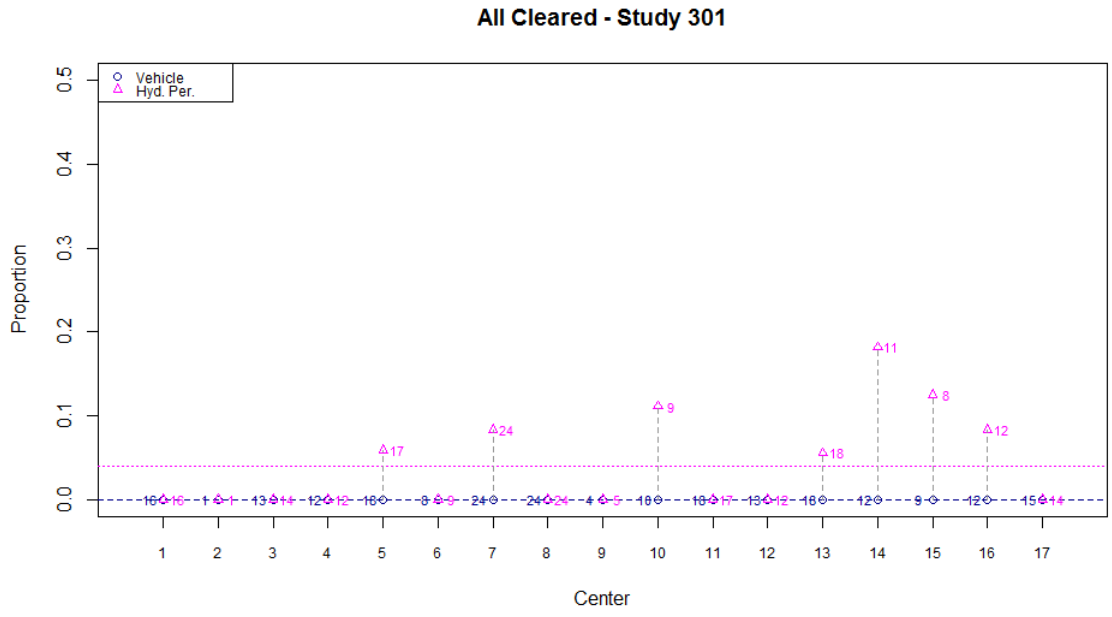
	Study 301		Study 302	
	HP N=223	Vehicle N=227	HP N=244	Vehicle N=243
1 or 2 lesions retreated	4/12 (33.3%)	--	3/18 (16.7%)	--
3 or 4 lesions retreated	5/206 (2.4%)	0/227 (0%)	10/220 (4.6%)	0/239 (0%)
Not retreated (all PLA=0 at Day 22)	0/1 (0%)	--	6/6 (100%)	--
Not retreated for other reasons	0/4 (0%)	--	--	0/4 (0%)

Source: 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

3.2.5 Efficacy by Center

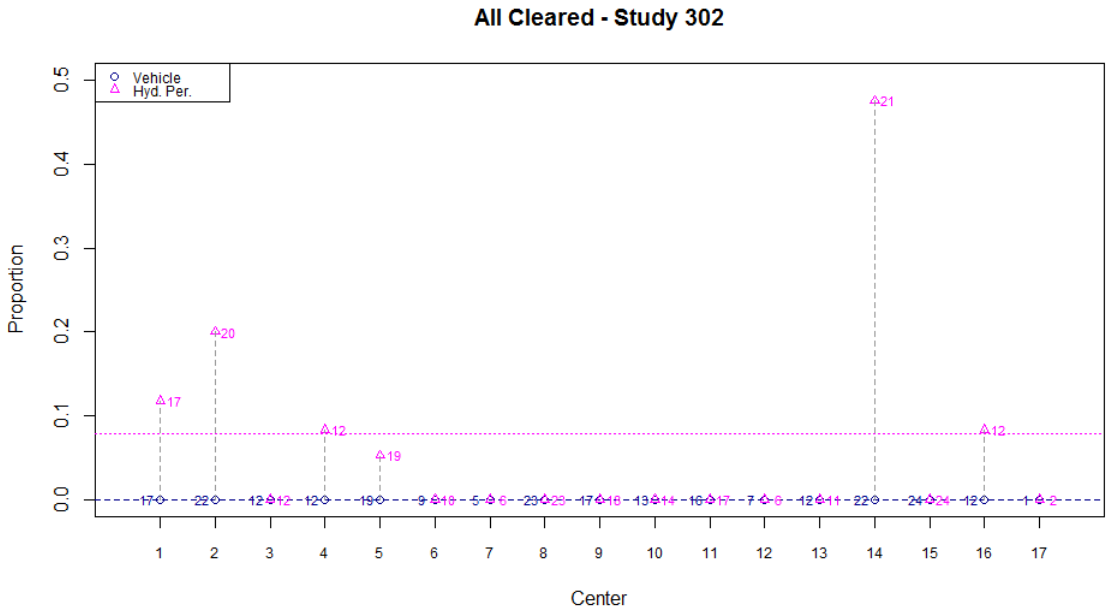
Study 301 and Study 302 were each conducted at 17 sites. The 9 hydrogen peroxide subjects with complete response in Study 301 were spread across 7 centers. However, in Study 302, out of the 19 subjects with complete response, 10 were from a single center while the other 9 were spread across 5 centers. See Figure 1 and Figure 2.

Figure 1 – Proportion of Subjects with All 4 Lesions Cleared by Study Center (Study 301)



Source: Reviewer analysis.

Figure 2 Proportion of Subjects with All 4 Lesions Cleared by Study Center (Study 302)



Source: Reviewer analysis.

The complete clearance rate among hydrogen peroxide subjects was higher in Study 302 than study 301 (8% vs. 4%). The higher complete clearance rate in Study 302 relative to Study 301 appears to be driven by the high rate of responders at Center 14 in Study 302. The response rate on the hydrogen peroxide arm at Center 14 was much higher than what was observed at the other centers (48% at Center 14 vs 4% for the other centers combined), and the sample size was among the higher sample sizes among the centers in the study. Over half of the responders in Study 302 (10/19) were enrolled at Center 14. The center with the next highest response rate was Center 2 with a 20% response rate (4/20). If the analysis for the complete response in Study 302 is conducted excluding Center 14, the point estimates are much closer to the results from Study 301 (4% vs. 0%), and are still statistically significant (p=0.002). See Table 12.

Table 12 – Complete Clearance Rate at Day 106 in Study 302 Excluding Center 14

	Study 302		
	Hyd. Per.	Vehicle	P-value
All Centers Except Center 14	9/223 (4.0%)	0/221 (0%)	0.002
Center 14	10/21 (47.6%)	0/22 (0%)	

Source: Reviewer analysis.

Center 14 in Study 302 was inspected by the Office of Scientific Investigations. According to the Clinical Inspection Summary (see review by Bei Yu dated 10/13/2017), no issues were identified Center 14 during the inspection:

For Protocol A-101-SEBK-302, 45 subjects were screened and 43 subjects were enrolled, all of whom completed the study. ICFs for all 45 screened subjects were reviewed to ensure that subjects were properly consented. Study records for all 43 randomized subjects were reviewed, including, but was not limited to, financial disclosure, training, protocol deviations, CRFs, monitor/IRB communications, and safety reports. The enrolled subjects met eligibility criteria, and the primary endpoint data were verifiable. There was no evidence of under reporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

The final classification of the investigator at Center 14 was No Action Indicated (NAI).

The results from Center 14 were also explored to see if the higher response rate was related to any differences due to the baseline lesion characteristics (baseline PLA, total lesion area, and number of facial lesions). See Table 13. However, the proportion of subjects with the various baseline disease classifications were similar in Center 14 and the other centers. The largest discrepancy was the baseline PLA category, and in that case Center 14 had a larger proportion of subjects with at least one lesion with PLA =3 than the other centers combined (86% vs. 65%). The results at Center 14 were consistently higher across all baseline lesion characteristic subgroups than the other centers combined. The higher response rate on the hydrogen peroxide arm does not appear to be driven by differences in baseline disease characteristics.

Table 13 – Complete Clearance Rate by Baseline Lesion Characteristics in Study 302

	Center 14		Other Centers	
	HP N=21	Vehicle N=22	HP N=223	Vehicle N=221
Baseline PLA				
All PLA = 2	3/4 (75.0%)	0/2 (0%)	4/78 (5.1%)	0/79 (0%)
At least one PLA = 3	7/17 (41.2%)	0/20 (0%)	5/145 (3.4%)	0/142 (0%)
Total Lesion Area				
≤ Median[a]	4/9 (44.4%)	0/11 (0%)	6/108 (5.6%)	0/117 (0%)
> Median	6/12 (50.0%)	0/11 (0%)	3/115 (2.6%)	0/104 (0%)
Number on Face				
1	5/13 (38.5%)	0/17 (0%)	4/184 (2.2%)	0/193 (0%)
2	4/6 (66.7%)	0/5 (0%)	2/27 (7.4%)	0/20 (0%)
3	1/2 (50.0%)	--	3/12 (25.0%)	0/8 (0%)

Source: reviewer analysis

Thus, although the complete response rate estimate in Study 302 is impacted by the high response rate at Center 14, statistical significance in Study 302 is maintained whether or not Center 14 is included in the analysis.

3.2.6 **Lesion Level Analyses**

All subjects had 4 treated lesions, at least one of which was on the face and one of which was on the trunk or extremities. Overall, 26% of lesions treated with hydrogen peroxide in Study 301 and 34% of lesions treated with hydrogen peroxide in Study 302 cleared. Facial lesions had the highest clearance rate followed by lesions on the trunk and lesions on the extremities. See Table 14.

Table 14 - Lesion Clearance Rates by Body Location (Lesion Level)

	Study 301		Study 302	
	Hyd. Per. N=879	Vehicle N=903	Hyd. Per. N=976	Vehicle N=944
Overall	225/879 (25.6%)	17/903 (1.9%)	332/976 (34.0%)	6/944 (0.6%)
Face	97/263 (36.9%)	10/278 (3.6%)	146/305 (47.9%)	4/276 (1.4%)
Trunk	114/502 (22.7%)	5/521 (1.0%)	165/583 (28.3%)	2/573 (0.3%)
Extremities	14/114 (12.3%)	2/104 (1.9%)	21/88 (23.9%)	0/95 (0%)

Source: Reviewer analysis.

Lesions that were thin (PLA=2) at baseline and treated with hydrogen peroxide solution had a clearance rate about 5-7% higher than lesions that were thick (PLA=3) at baseline within each study. Similarly, the clearance rate in smaller lesions (less than or equal to the baseline median size) was about 5-7% higher than for the larger lesions (greater than the baseline median size). See Table 15.

Table 15 - Lesion Clearance Rates by Baseline PLA and Lesion Area (Lesion Level)

	Study 301		Study 302	
	Hyd. Per. N=879	Vehicle N=903	Hyd. Per. N=976	Vehicle N=944
Baseline PLA				
PLA=2	185/677 (27.3%)	13/674 (1.9%)	228/635 (35.9%)	5/609 (0.8%)
PLA=3	40/202 (19.8%)	4/229 (1.8%)	104/341 (30.5%)	1/335 (0.3%)
Baseline Area				
≤ Median[a]	130/446 (29.2%)	11/478 (2.3%)	174/473 (36.8%)	5/494 (1.0%)
> Median	95/433 (21.9%)	6/425 (1.4%)	158/503 (31.4%)	1/450 (0.2%)

[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: Reviewer analysis.

3.3 Evaluation of Safety

3.3.1 **Extent of Exposure**

All subjects had all 4 lesions treated at baseline. At Day 22, more than 90% of subjects had 3 or 4 lesions retreated, 6% of hydrogen peroxide subjects had 1 or 2 lesions treated, and approximately 2% of subjects did not receive the second treatment (due to either complete clearance on Day 22, dropout, or otherwise did not receive the second treatment). See Table 16.

Table 16 –Treatments Received

	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: reviewer analysis.

3.3.2 Local Skin Reactions

Local skin reactions were actively assessed on a 4-point scale (none, mild, moderate, severe) throughout the study. Pruritus and stinging were evaluated by the subject at each visit (average severity over the past 24 hours) and 10 minutes after treatment at baseline and Day 22. Erythema, edema, scaling/dryness, vesicles/bullae, crusting, erosion, ulceration, post-inflammatory hyperpigmentation, post-inflammatory hypopigmentation, atrophy, and scarring were assessed by the investigator at each visit. In addition, erythema, edema, scaling/dryness, and vesicles/bullae were assessed 20 minutes post-treatment at baseline and Day 22. Most subjects receiving hydrogen peroxide experienced local skin reactions. More than 10% of subjects experienced severe stinging, edema, and erythema during the trials. See Table 17.

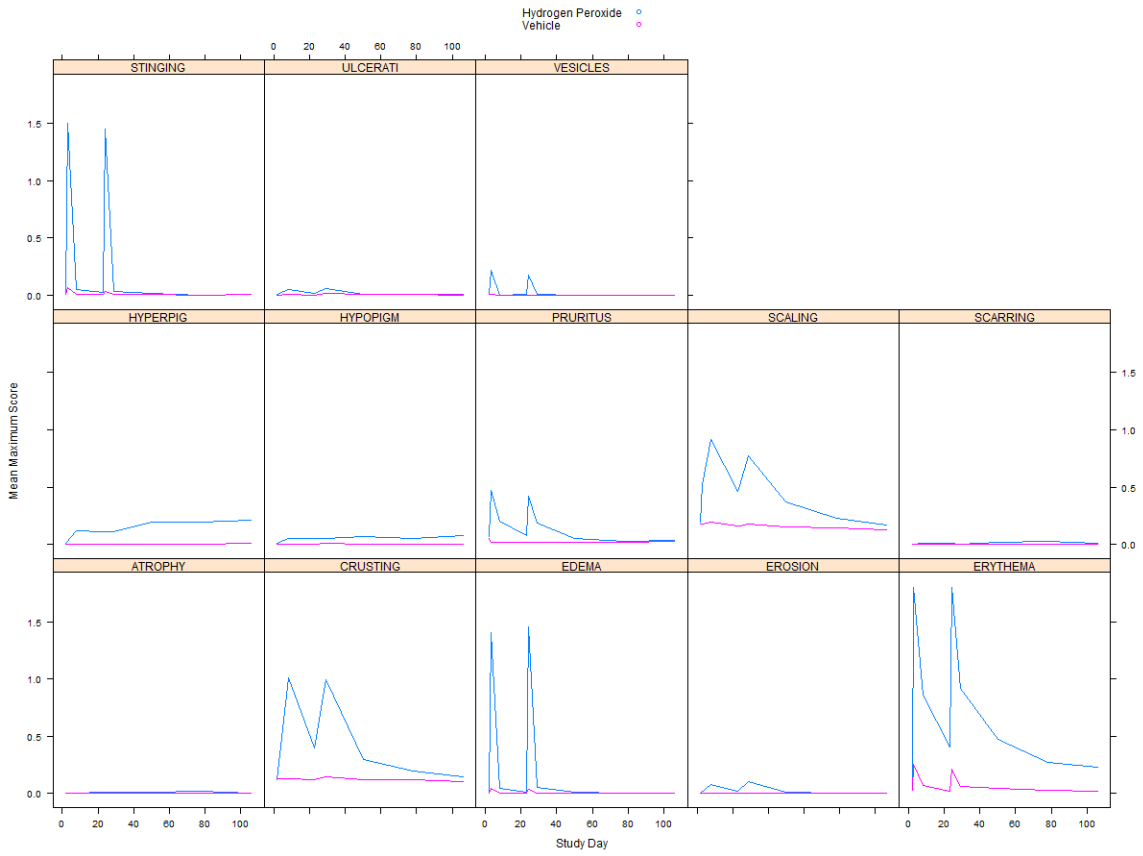
Table 17 – Maximum Post-Baseline Local Skin Reaction Rating through Day 106 (Studies 301 and 302 pooled)

	Hydrogen Peroxide N=467				Vehicle N=470			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Pruritus	42.2%	34.1%	18.4%	5.4%	91.9%	6.8%	1.1%	0.2%
Stinging	2.8%	33.6%	49.0%	14.6%	90.4%	8.7%	0.6%	0.2%
Atrophy	95.5%	4.5%	0%	0%	100%	0%	0%	0%
Crusting	19.3%	34.1%	38.3%	8.4%	81.2%	13.0%	4.7%	1.1%
Edema	9.0%	28.1%	48.2%	14.8%	93.8%	5.5%	0.6%	0%
Erosion	85.2%	12.2%	1.9%	0.6%	99.4%	0.6%	0%	0%
Erythema	0.9%	13.3%	67.0%	18.8%	66.2%	28.5%	5.1%	0.2%
Hyperpigmentation	61.2%	31.9%	6.6%	0.2%	98.5%	1.3%	0.2%	0%
Hypopigmentation	80.7%	16.3%	2.8%	0.2%	98.9%	0.9%	0.2%	0%
Scaling	10.5%	49.0%	35.8%	4.7%	66.8%	27.7%	4.9%	0.6%
Scarring	96.8%	2.6%	0.4%	0.2%	100%	0%	0%	0%
Ulceration	91.4%	6.4%	1.9%	0.2%	98.3%	0.9%	0.9%	0%
Vesicles	75.6%	20.8%	3.0%	0.6%	99.6%	0.4%	0%	0%

Source: reviewer analysis

Stinging, pruritus, vesicles, edema, and erythema all peaked right after treatment. Scaling and crusting, and erosion were most common 1 week post-treatment. The means of the maximum score per subject at each visit are presented in Figure 3.

Figure 3 – Mean Maximum Local Skin Reaction Score by Visit (Pooled Studies)



Source: Reviewer analysis

3.3.3 Adverse Reactions

Other than local skin reactions,19-24% of hydrogen peroxide subjects and 18-20% of vehicle subjects reported adverse events. No spontaneously reported adverse event occurred in more than 3% of subjects per arm. The most common adverse events were nasopharyngitis and sinusitis. See Table 18.

Table 18 – Adverse Events occurring in at least 1% of Subjects in either Arm

	Study 301		Study 302	
	HP N=223	Vehicle N=227	HP N=244	Vehicle N=243
Adverse Events	54 (24%)	45 (20%)	46 (19%)	43 (18%)
Nasopharyngitis	7 (3%)	3 (1%)	1 (<1%)	3 (1%)
Sinusitis	--	1 (<1%)	4 (2%)	4 (2%)
Bronchitis	1 (<1%)	3 (1%)	2 (<1%)	1 (<1%)
Upper resp. tract inf.	3 (1%)	1 (<1%)	--	2 (<1%)
Actinic keratosis	--	3 (1%)	1 (<1%)	--
Seasonal allergy	3 (1%)	--	1 (<1%)	--
Herpes zoster	--	1 (<1%)	3 (1%)	--

Source: pg 119-123 of Study A-101-SEBK-301 Study Report Body and pg 120-124 of Study A-101-SEBK-302 Study Report Body

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, Age, and Geographic Region

Treatment effects were generally consistent across age groups, gender, race, and ethnicity, although nearly all subjects were white and not Hispanic or Latino. See Table 19. All subjects were enrolled in the United States.

Table 19 – Complete Clearance Rate by Subgroups

	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 Afric.-Amer.	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: Reviewer analysis

4.2 Other Special/Subgroup Populations

Not applicable.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The applicant evaluated the efficacy of hydrogen peroxide solution in the two vehicle-controlled studies for the treatment of seborrheic keratoses. Both studies had statistically significant results for the primary efficacy endpoint of complete clearance of all target lesions. The secondary endpoint of at least 3 out of 4 target lesions achieved complete clearance also achieved statistical significance in both studies. The proportion of subjects with missing data was small (<2%) and the results were not impacted by the handling of missing data. In Study 302, the response rate on the hydrogen peroxide arm was nearly twice the response rate observed in Study 301. The higher response rate in Study 302 was driven by the results at a single center, as this center enrolled about 9% of the total subjects, but includes 53% of the subjects who achieved complete clearance. However, if the center with the high proportion of responders is removed from the analysis, the response rate from the remaining centers is similar to the response rate observed in Study 301. The results of Study 302 remain statistically significant even after removing the center with the high proportion of responders.

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

Local skin reactions were common with stinging, pruritus, vesicles, edema, and erythema all peaking after treatment and then subsiding over time.

5.2 Conclusions and Recommendations

Hydrogen peroxide solution was superior to vehicle solution in the treatment of seborrheic keratoses. Studies 301 and 302 enrolled subjects age 18 and older with a clinical diagnosis of stable clinically typical SK and 4 appropriate SK target lesions on the trunk, extremities, and face. At least 1 target lesion was to be on the trunk or extremities and at least 1 target lesion was to be on the face. Each target lesion was to be discrete, with length 5-15 mm, width 5-15 mm, and thickness ≤ 2 mm. At baseline target lesions were to have PLA ≥ 2 (thin or thick). The primary endpoint of complete clearance of all target lesions at Day 106 and the secondary endpoint of at least 3 out of 4 target lesions achieving complete clearance at Day 106 demonstrated efficacy in both studies. See Table 20.

Table 20 - Primary and Secondary Endpoints at Day 106 (ITT, Non-Responder Imputation)

	Study 301			Study 302		
	Hyd. Per. N=223	Vehicle N=227	P-value	Hyd. Per. N=244	Vehicle N=243	P-value
All 4 lesions clear	9 (4.0%)	0 (0%)	0.002	19 (7.8%)	0 (0%)	<0.001
≥ 3 lesions clear	30 (13.5%)	0 (0%)	<0.001	56 (23.0%)	0 (0%)	<0.001

5.3 Labeling Recommendations

The applicant proposed only including adverse reaction information based on spontaneously reported adverse reactions. However, as the most common adverse reactions (local skin reactions) were actively assessed, information on local skin reactions should also be included in labeling.

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, Ph.D.
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