CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208081Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208081
Drug Name:	AMELUZ® gel, 10%, in combination with photodynamic therapy (PDT) using the BF-RhodoLED lamp
Indication(s):	Treatment of subjects with mild to moderate severe actinic keratosis on the face and scalp
Applicant:	Biofrontera Bioscience GmbH
Date(s):	Stamp date: 7/10/2015 PDUFA: 5/10/2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Carin Kim, Ph.D.
Concurring Reviewers:	Mohamed Alosh, Ph.D.
Medical Division:	Division of Dermatology and Dental Products (DDDP)
Clinical Team:	Denise Cook, M.D. Gordana Diglisic, M.D.
Project Manager:	Paul Phillips

Keywords:
Actinic Keratosis (AK); Photodynamic Therapy (PDT); Superiority; Non-inferiority

Table of Contents

1. EXECUTIVE SUMMARY

BF-ALA 200 (Ameluz®) gel was superior to vehicle gel in the treatment of **mild to moderate** actinic keratosis (AK) on the face and/or scalp in three Phase 3 trials, ALA-AK-CT002, ALA-AK-CT003, and ALA-AK-CT007 (from hereon denoted as Trials 02, 03, and 07). The trials enrolled male or female subjects between 18 and 85 years of age (inclusive), with 4-8 clinically confirmed AK target lesions of mild to moderate intensity within the face or bald scalp excluding eyes, nostrils, ears and mouth, (i.e., AK grade I or II according to Olsen *et al*., 1991) at baseline.

The protocol-specified primary efficacy endpoint for all three trials was the overall patient complete response assessed 12 weeks after the last photodynamic therapy (PDT), and an overall complete responder was defined as a patient, in whom all treated lesions were cleared, including patients receiving the second treatment, if necessary. Efficacy results for the primary endpoint were statistically significant for all three trials (p-value< 0.0001). As Trials 02 and 03 used PDTs from both narrowband as well as broadband spectrum, Table 1 presents the efficacy results for the primary endpoint, the overall patient complete response assessed 12 weeks after the last PDT, and the efficacy results by the light source (i.e., narrow vs. broad) as well.

Table 1. Proportion of subjects achieving Complete Clearance 12 weeks after the last photodynamic therapy (PDT)

Trial 02			
	Ameluz N=248	Vehicle N=76	Metvix N=246
Complete Clearance	194 (78%)	13 (17%)	158 (64%)
p-value	< 0.0001(1)		N/A
By light source			
Narrow	106/125 (85%)	5/39 (13%)	85/126 (67%)
Broad	88/123 (72%)	8/37 (22%)	73/119 (61%)

	Trial 03		**Trial 07**	
Light Source	Ameluz N=81	Vehicle N=41	Ameluz N=55	Vehicle N=32
Complete Clearance	53 (65%)	5 (12%)	50/55 (91%)	7/32 (22%)
p-value	< 0.0001(2)		< 0.0001 (3)	
By light source				
Narrow	27/32 (84%)	2/16 (13%)	50/55 (91%)	7/32 (22%)
Broad	26/49 (53%)	3/25 (12%)	N/A	

Source: reviewer's table; (1) p-value from Chi-square test; (2) p-value from CMH test stratified by center; (3) p-value from Fisher's Exact Test. The primary imputation method was the last observation carried forward (LOCF).

For Trial 02, following the comparison of Ameluz vs. vehicle, if statistically significant, the applicant's testing hierarchy called for comparing the Ameluz to Metvix using non-inferiority (NI) testing with the NI margin of 15%. The lower-bound of the one-sided

97.5% confidence interval was greater than -15%, and the applicant concluded non-inferiority of Ameluz compared to Metvix; however, it should be noted that Metvix was not used at the approved U.S.-labeled dose. According to the FDA-approved label, Metvix was approved to be used with Aktilite CL128 lamp, and requires two PDTs, 1 week apart. In Trial 02, the PDT for Metvix included broadband (Waldmann, Hydrosun Photodyn lamps) as well as narrowband (Omnilux, Aktilite lamps) light sources, and those randomized to Metvix did not receive a 2nd PDT one week after the 1st PDT. Thus, with such differences in the lamp types and the number of PDT treatments, comparison of Ameluz against Metvix would not be appropriate. Further, for a comparative claim, generally two active-controlled Phase 3 trials would be required which comment was conveyed to the sponsor at the Pre-IND meeting (7/11/2012). Consequently, any findings from such comparison would be exploratory at best.

Each Phase 3 trial listed several secondary endpoints including the proportion of subjects or AK lesions with complete clearance after each assessment, partial response assessed 12 weeks after the last PDT, overall cosmetic outcome after the last PDT, among other endpoints. However, for the analysis of the secondary endpoints, the list and the order of the secondary endpoints across the three Phase 3 trials were different, and given the lack of multiplicity adjustment plan to control the Type I error rate in Trials 02 and 03, there was no replication of study findings for secondary endpoints across the three Phase 3 trials.

2. INTRODUCTION

2.1 Overview

The applicant submitted results from three Phase 3 trials (Trials 02, 03, 07) to support the efficacy and safety of Ameluz gel for the treatment of **mild to moderate** actinic keratosis (AK) on the face and scalp. None of the trials were conducted in the United States.

It should be noted that Trial 02 was an observer-blind trial, because of the differences in formulation between the Ameluz and its vehicle gel, vs. Metvix cream. The sponsor stated that "to ensure an observer-blind conduct of the study, the application of the investigative products (IPs) and the illumination were not done by the investigator assessing the lesions but by other qualified study personnel".

According to the sponsor, with Trial 07, the sponsor planned to bridge the study results obtained in the previous trials with narrow spectrum LED lamps (Aktilite CL 128 or Omnilux PDT) with BF-RhodoLED.

Table 2 provides an overview of the applicant's Phase 3 trials.

Table 2. Overview of the Applicant's Phase 3 trials

	ALA-AK-CT002 (Trial 02)	ALA-AK-CT003 (Trial 03)	ALA-AK-CT007 (Trial 07)
Study design	Randomized, **observer-blind**, multinational Phase 3 trial to evaluate the safety and efficacy of a nanoemulsion gel formulation Ameluz, in comparison with Metvix and placebo, for the treatment of AK with PDT	Randomized, double-blind, placebo-controlled, inter-individual, 2-armed, multicenter study using Ameluz and placebo	Randomized, double-blind, placebo-controlled, inter-individual, 2-armed, multicenter study using Ameluz and placebo
Dates	4/21/2008-5/11/2010	12/13/2007-10/01/2008	10/4/2013-8/15/2014
Treatment	4-8 single AK lesion (up to 20 cm^2)	4-8 single AK lesion (up to 20 cm^2)	Field treatment of 4-8 AK lesions (20 cm^2)
Number of Centers	23 centers in Germany 2 centers in Austria 1 in Switzerland	8 centers in Germany	7 centers in Germany
Number of subjects	571 randomized in 3:3:1 ratio: • 248 Ameluz • 247 Metvix • 76 Placebo	122 randomized in 2:1 ratio: • 81 Ameluz • 41 Placebo	87 randomized in 2:1 ratio: • 55 in Ameluz • 32 in Placebo
Lamps	Narrow • Aktilite CL 128 • Omnilux PDT Broad • Waldman PDT 1200L • HydroSun Photodyn 505 or 750	Narrow • Aktilite CL 128 Broad • Hydrosun Photodyn 750	Narrow • BF-RhodoLED

Source: An excerpt from the sponsor's submission

2.2 Regulatory History

The clinical development program for Ameluz for the treatment of AK for face and scalp was under IND 115412. There were two meetings with the sponsor: a Pre-IND meeting on 7/11/2012 to discuss the development program for Ameluz, and a Pre-NDA meeting on 10/18/2014 to discuss their planned NDA submission.

At the Pre-IND meeting (7/11/2012), in response to the sponsor's question regarding the adequacy of the completed Phase 3 trials (Trials 02 and 03) for the registration of Ameluz for the indication of AK, the Agency responded as below:

- "The design of trials ALA-AK-CT002 and CT003 appear reasonable. However, as the trials are already completed, the Division cannot make any agreements.
- It should be noted that for trials to establish efficacy, trials need to have appropriate agreed-upon endpoints with detailed, pre-specified statistical analysis plans that include multiplicity adjustments to control for the Type I error rate, as well as a scientifically sound method for handling missing data along with sensitivity analyses to ensure that efficacy is not driven by the chosen imputation

method. Furthermore, for multicenter Phase 3 trials, the Division is interested in checking the consistency of treatment effect across centers.
- It should also be noted that for a comparative claim, generally two active-controlled Phase 3 trials will be required.
- The applicability of foreign data to the U.S. population will also be a review issue. You are referred to the guidance, Acceptance of Foreign Clinical Studies."

At the Pre-NDA meeting (10/18/2014), the Agency provided comments regarding the format of the NDA submission. According to the sponsor, Ameluz was approved in the European Union in December 2011 for the treatment of AK of mild to moderate intensity.

2.3 Data Sources

This reviewer evaluated the applicant's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted. The datasets in this review are archived at: \\cdsesub1\evsprod\nda208081\0000\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted electronic analysis datasets for review, and no requests for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

For Trial 02, a total 571 subjects from 26 centers were randomized in a 3:3:1 ratio to the following arms:
- Ameluz (BF-200 ALA) gel
- Metvix cream
- Placebo gel.

One hundred twenty two subjects from 8 centers and 87 subjects from 7 centers in Trials 03 and 07, respectively, were randomized in a 2:1 ratio to the following arms:
- Ameluz (BF-200 ALA) gel
- Placebo gel.

For randomization, according to the protocol, a block randomization scheme was generated using Accovion GmbH using Rando® (block size not specified in the protocols) for Trials 02 and 07, and for Trial 03, the randomization scheme was prepared by the Statistical Department of FOCUS using RANUNI for uniformly distributed variables with a block size of 6. While randomization was not stratified by center for

Trial 02, the protocol for Trial 07 specified that randomization was stratified by center, and the SAP for Trial 03 specified that each center was supplied with the investigational medicinal products (IMP) for 12 subjects.

For enrollment for all three Phase 3 trials, male or female subjects between 18 and 85 years of age (inclusive), with 4-8 clinically confirmed AK target lesions of mild to moderate intensity within the face or bald scalp (excluding eyes, nostrils, ears and mouth) were enrolled. The AK grade I or II according to Olsen et al., 1991, were used as shown below:

- **Mild / Grade I AK lesions** should present a flat, pink maculae without signs of hyperkeratosis and erythema. The lesions should be slightly palpable, with AK better felt than seen.
- **Moderate / Grade II AK lesions** should present as pink to reddish papules and erythematous plaques with hyperkeratotic surface. These AK lesions should be moderately thick and can be easily seen and felt.
- **Severe / Grade III AK lesions** should present as very thick plaques with hyperkeratotic surface. These AK lesions should be very thick and/or obvious.

Source: protocol for Trial 02 (page 46).

The protocols for all three trials specified that if AK lesions were present on both face and on the bald scalp, illuminations would occur separately for these two areas. In this case, the gel was applied to one of the areas with a delay of at least 15 minutes to allow for the irradiation of the two areas one after the other. A maximum of two consecutive irradiation cycles on two different areas was allowed.

After determining the numbers, location and size of all target AK lesions within the face (target area A) and/or the bald scalp (target area B), all scabs, crusts or hyperkeratosis of each AK lesion in the treatment area were thoroughly removed. In addition, all lesion surfaces were scraped gently using a curette or scalpel blade. Before applying Ameluz, all lesions were wiped with ethanol or isopropanol-soaked cotton pad to ensure degreasing of the skin. Ameluz was applied using glove protected fingertips or a spatula approximately 1mm thick and approximately 5 mm of the surrounding skin. The gel was allowed to be dried for approximately 10 minutes before applying occlusive dressing. Then the area where the gel was applied with occlusive dressing was covered for 3 hours. After 3 hours, the dressing was removed and the remaining gel was wiped off. Immediately after removing the occlusion and any remaining gel, the area of the skin was illuminated.

Ameluz gel or vehicle (or Metvix for Trial 02) was applied 3 hours prior to the 1st Photodynamic therapy (PDT). Subjects still showing target lesions at Week 12 (i.e., not completely cleared) were re-treated with the assigned investigative product at Week 12, 3 hours prior to their second PDT.

The primary efficacy endpoint for all three trials was the overall patient complete response assessed 12 weeks after the last PDT, and an overall complete responder was

defined as a patient in whom all treated lesions were cleared, after the first PDT or after the second PDT.

The list and the order of secondary endpoints across the three Phase 3 trials were different. Table 3 summarizes the primary and the secondary endpoints across the three Phase 3 trials. It should be noted that the secondary efficacy variables in Trial 02 were analyzed descriptively, and were exploratory in nature (page 19, SAP). For Trial 03, there was no prespecified multiplicity adjustment plan for the secondary endpoints. For Trial 07, the sponsor specified sequentially testing the pre-defined order of secondary endpoints to ensure the family wise error rate (FWER) (protocol, page 68); however, given the lack of plan for multiplicity adjustment to control the Type I error rate in Trials 02 and 03, there is no replication of study findings for secondary endpoints from the three Phase 3 trials.

Table 3. Endpoints Comparison across the three Phase 3 trials:

		Trial 02	**Trial 03**	**Trial 07** (1)
Primary		Overall patient complete response rate assessed 12 weeks after the last PDT		
Secondary	**1**			Patient histological confirmed response (HCR) rate
	2	Subject complete response (complete clearance of all treated lesions) at each assessment	Proportion of subjects with complete clearance after the first treatment	Patient complete response assessed 12-weeks after the first PDT
	3	Lesion complete response (completely cleared individual lesions) at each assessment	Proportion of AK lesions showing complete remission at Week 12 after the last PDT	Lesion complete response assessed 12 weeks after the last PDT
	4	Subject partial response (complete clearance of at least 75% of the treated lesions) at each assessment	Proportion of subjects with clearance of at least 75% of lesions after the first treatment and 12 weeks after the last PDT	Patient partial response assessed 12 weeks after the last PDT
	5	Reduction of total lesion area per subject at each assessment	Reduction of total lesion area within the target treatment area per subject at Week 12 after the last PDT	Reduction of total lesion area per patient, 12 weeks after the last PDT
	6	The overall cosmetic outcome 12 weeks after the last PDT	The overall cosmetic outcome 12 weeks after the last PDT	Overall cosmetic outcome 12 weeks after the last PDT
	7	The change in skin quality assessments compared to baseline assessed 12 weeks after the first and 12 weeks after the last PDT	Change in skin quality assessment compared to baseline of all target lesions located within the target treatment area	Skin quality assessment from baseline to 12 weeks after the last PDT (tertiary endpoint)

(1) Secondary endpoints for Trial 07 were analyzed in the hierarchical order.
Source: An excerpt from the sponsor's previous submission

The primary analysis population was defined slightly different across the three trials. For Trial 02, the ITT was the primary analysis set, and it was defined as "all randomized subjects and treated at least once with investigation product after randomization.

Treatment with investigational product consists of application of study drug followed by illumination". For Trial 03, the protocol specified that the Full Analysis Set (FAS) was the primary analysis set, and that the FAS was as close to the Intent-to-Treat principle as possible, defined as all subjects who received treatment and had at least one post-dose assessment of the clearance of the AK lesions in the target area of the primary variable. For Trial 07, a similarly defined analysis set as that in Trial 02, denoted as FAS, was the primary analysis set.

As with the definition of the primary analysis set in the three Phase 3 trials, the definitions for the Per Protocol (PP) set slightly varied across the three trials as summarized below.

For Trial 02, the PP set was defined as below:

- All target lesions have grade I or II according to Olsen at baseline
- AK confirmed by biopsy of a representative lesion taken at screening
- AK lesion assessment $\geq$ 9 weeks after the last PDT available
- Treated with the same investigational product in PDT-1 and PDT-2 – this may by chance still be true even if a treatment kit with a wrong randomization number was used
- Incubation time of at least 2:00 hours
- Treatment with a separate tube of study medication for PDT-1 and PDT-2
- No forbidden treatment or surgical procedures in the treatment areas
- No forbidden concomitant medications or therapies defined as such that are not likely to affect the outcome due to the application regime (timing, dose, location)
- The shelf life of the study medication was not expired before treatment

For Trial 03, the PP set was defined as all subjects who had no significant protocol violations, and for whom clearance of all lesions present at baseline could be assessed after 12 weeks of treatment.

For Trial 07, the PP set was defined as those subjects that fulfilled all of the following criteria:

- Treated with the study medication according to the randomization plan.
- All target lesions were grade I or II according to Olsen criteria at baseline.
- AK confirmed by biopsy of a representative lesion taken at screening.
- At least one AK lesion assessment was available, i.e. after PDT-1 or if retreated, after PDT-2.
- Evaluation of the second biopsy at the end-of-study visit that did not result in a diagnosis of BCC or SCC.
- No concomitant medications or therapies that might have an impact on the efficacy or safety analyses. The terms were identified during the blind data review meeting before database closure.
- Treatment with BF-RhodoLED lamp.

For the analysis of the primary endpoint, the protocol for Trial 02 specified using the Chi-square test with a two-sided significance level of 0.05. As randomization was not stratified by center, the sponsor's approach was reasonable. For Trials 03, the protocol specified using the CMH test stratified by site as the primary analysis method, and the protocol for Trial 07 specified using the Fisher's Exact test as the primary analysis method.

For handling of missing data, the sponsor used the last observation carried forward (LOCF) as the primary imputation method. It should be noted that the missing data in each trial was minimal.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

For Trial 02, a total of 7 (3%) Ameluz-treated subjects, 8 (11%) vehicle-treated subjects, and 7 (3%) Metvix-treated subjects discontinued the trial. According to the applicant's study report, the majority of the discontinued subjects in the vehicle arm were due to "subject's decision" or "lack of efficacy". Subject disposition table for Trials 02 is presented in Table 4.

Table 4. Subject Disposition for Trial 02

Trial 02			
	Ameluz N=248	Vehicle N=76	Metvix N=247
ITT	248	76	246[(1)]
Discontinued	7 (3%)	8 (11%)	7 (3%)
Reasons for discontinuation			
Subject's decision	4	4	3
AE	2	0	2
Lack of efficacy	0	2	0
Lost to follow-up	1	1	0
Protocol violation	0	0	2
Other	0	1	1

Source: Applicant's table; (1) Subject 115/10 did not receive PDT

For Trial 03, a total of 4 (5%) Ameluz-treated subjects, and 4 (10%) vehicle-treated subjects discontinued the trial. According to the applicant's Appendix 16.2.1.1, the four vehicle-treated subjects that withdrew experienced lack of efficacy. For Trial 07, there was a total of 6 placebo subjects (19%) that discontinued the trial, 5 of which were classified as "patient's decision". The study reported did not provide any further information regarding the decisions to discontinue the trial. Subject disposition for Trials 03 and 07 are in Table 5.

For imputing the missing values due to the lack of response or adverse events in the vehicle arm, the primary imputation method of the last observation carried forward (i.e., non-responses), may be justified.

Table 5. Subject Disposition for Trials 03 and 07

	Trial 03		Trial 07	
	Ameluz	Vehicle	Ameluz	Vehicle
ITT	81	41	55	32
Applicant's FAS	80	40	55	32
Discontinued	4 (5%)	4 (10%)	1 (2%)	6 (19%)
Reasons for discontinuation				
Protocol deviation	1	0	0	0
Adverse Event	0	0	0	0
Lack of tolerability	0	0	0	0
Loss to follow-up	0	0	1	1
Other	3	4 (1)	0	0
Patient's decision	0	0	0	5 (2)

Source: Applicant's table; (1) Appendix 16.2.1.1 specified that these subjects had "insufficient outcome of treatment", or "therapy not successful"; (2) the study report did not include further explanation regarding the patient's decisions.

For Trials 02 and 03, the applicant excluded the following 2 subjects in each trial from the efficacy analyses. For Trial 02, the following two subjects switched the lamp sources from PDT-1 to PDT-2, and were excluded from the efficacy analyses:

- Subject # 109/20 that received Ameluz switched from Omnilux to Aktilite
- Subject #109/10 that received Metvix switched from Omnilux to Waldmann.

For Trial 03, the applicant excluded 1 subject (ALA-AK-CT003/05-917) in Ameluz and 1 in vehicle (ALA-AK-CT003/06-908) because they did not receive post-baseline AK assessments after the first PDT. However, the above subjects were considered in the reviewer's ITT set for efficacy analyses.

Tables 6 and 7 present the baseline demographics and disease characteristics for Trials 02, and 03 and 07, respectively. The baseline demographics were generally balanced across the treatment arms for all trials. The majority of the subjects were male (approximately 86%) and all subjects were Caucasian in all three trials. The mean age of subjects was approximately 70 years (range 39 years to 87 years). Most subjects had moderate AK severity based on the Olsen scale (82%), Fitzpatrick skin type I, II or III (90%), and the majority of subjects (72%) had the AK on the face and/or forehead.

Table 6. Baseline demographic and disease characteristics for Trial 02

Trial 02			
	Ameluz N=248	Vehicle N=76	Metvix N=246
Age			
mean ± SD	70.2 ± 7.2	71.5 ± 6.7	71.0 ± 6.9
Range	39, 87	51, 84	44, 85
Gender			
Male	214 (86%)	60 (79%)	205 (83%)
Female	34 (14%)	16 (21%)	41 (17%)
AK severity			
Mild	39 (16%)	14 (18%)	41 (17%)
Moderate	209 (84%)	62 (82%)	205 (83%)
Fitzpatrick skin type			
I	3 (1%)	2 (3%)	6 (2%)
II	90 (36%)	27 (36%)	82 (33%)
III	118 (48%)	43 (57%)	133 (54%)
IV	35 (14%)	4 (5%)	23 (9%)
V, VI	2 (1%)	0	2 (1%)
Location of AK			
Treatment Area A (face/forehead)	149 (60%)	39 (51%)	138 (56%)
Treatment Area B (scalp)	67 (27%)	21 (28%)	58 (24%)
Both A and B	32 (13%)	16 (6%)	50 (20%)

Source: Reviewer table

Table 7. Baseline demographic and disease characteristics for Trials 03 and 07

Trial 03			Trial 07	
	Ameluz	Vehicle	Ameluz	Vehicle
ITT	81 (1)	41 (1)	55	32
Age				
mean ± SD	70.4 ± 5.2	70.8 ± 6.7	71.9 ± 6.4	71.0 ± 6.4
Range	58, 82	57, 85	56, 84	51, 84
Gender				
Male	72 (90%)	41 (78%)	50 (91%)	29 (91%)
Female	8 (10%)	9 (23%)	5 (9%)	3 (9%)
AK severity				
Mild	20 (25%)	12 (29%)	11 (20%)	7 (22%)
Moderate	61 (75%)	29 (71%)	44 (80%)	25 (78%)
Fitzpatrick skin type				
I	5 (6%)	1 (2%)	1 (2%)	-
II	42 (52%)	29 (71%)	28 (51%)	12 (38%)
III	32 (40%)	11 (27%)	19 (35%)	19 (59%)
IV	2 (3%)	-	6 (11%)	1 (3%)
V	-	-	1 (2%)	-
Location of AK				
Treatment Area A (face/forehead)	50 (62%)	26 (63%)	32 (58%)	17 (53%)
Treatment Area B (scalp)	22 (27%)	11 (27%)	22 (40%)	14 (44%)
Both A and B	9 (11%)	4 (10%)	1 (2%)	1 (3%)

Source: Reviewer table; (1) the applicant excluded 1 subject (ALA-AK-CT003/05-917) in Ameluz and 1 in vehicle (ALA-AK-CT003/06-908) because they did not receive post-baseline AK assessments after the first PDT. It should be noted that the above subjects were considered in the reviewer's ITT set for efficacy analyses.

3.2.3 Results and Conclusions

3.2.3.1 Efficacy Results

3.2.3.1.1 Trial 02

For Trial 02, for the primary endpoint, the Ameluz was superior to vehicle using the protocol-specified analysis method of Chi-square test with a 2-sided significance level of 0.05 (p-value< 0.0001). The complete clearance rates at 12 weeks after the last PDT by light source (narrow vs. broad), as well as by lamp types (Omnilux, Aktilite, Waldmann, Hydrosun Photodyn) are presented in Table 8. Further, efficacy results are also presented by the 1st or 2nd PDT (if not cleared by the 1st PDT).

For Trial 02, the treatment effects from of the narrowband PDTs were 64% and 75% for the Omnilux and Aktilite lamps, respectively, and for the broadband PDTs, the treatment effects were 87% and 45% for the Waldmann and Hydrosun Photodyn lamps, respectively. Note that given the small number of subjects that were treated with the Waldmann lamp (15 in Ameluz, and 3 in vehicle); it will be difficult to draw any conclusion for subjects that were treated with the Waldmann lamp. For all lamps except the Omnilux, the complete clearance rates at 12 weeks after the 1st PDT were similar to those after the 2nd PDT. Table 8 presents primary efficacy results for Trial 02.

Table 8. Complete clearance at 12 weeks after the last PDT by light source, lamp type, and PDT (Trial 02)

Trial 02				
Light Source		Ameluz N=248	Vehicle N=76	Metvix N=246(1)
Narrow		106/125 (85%)	5/39 (13%)	85/126 (67%)
Broad		88/123 (72%)	8/37 (22%)	73/119 (61%)
Light Source	Lamp Type	BF200ALA	Vehicle	Metvix
Narrow	Omnilux	32/35 (91%)	3/11 (27%)	23/31 (74%)
	1st PDT	17/36 (47%)	0/11 (0%)	9/31 (29%)
	2nd PDT	15/18 (83%)	3/11 (27%)	14/22 (63%)
	Aktilite	74/90 (82%)	2/28 (7%)	62/96 (65%)
	1st PDT	50/89 (56%)	0/28 (0%)	39/96 (41%)
	2nd PDT	23/39 (59%)	2/28 (7%)	23/57 (40%)
Broad	Waldmann	13/15 (87%)	0/3 (0%)	12/13 (92%)
	1st PDT	10/15 (67%)	0/3 (0%)	8/13 (62%)
	2nd PDT	3/5 (60%)	0/3 (0%)	4/5 (80%)
	Hydrosun Photodyn	75/108 (69%)	8/34 (24%)	61/106 (58%)
	1st PDT	43/108 (40%)	3/34 (9%)	35/106 (33%)
	2nd PDT	32/65 (49%)	5/31 (16%)	26/71 (37%)

Source: Reviewer's table; (1) Subject # 109/20 that received BF200ALA switched from Omnilux to Aktilite; Subject #109/10 that received Metvix switched from Omnilux to Waldmann; as the subject switched from narrow to broad, this subject was neither classified as "narrow" nor "broad".

Per the protocol-specified hierarchical testing, the Ameluz was then compared to Metvix using non-inferiority (NI) testing with the NI margin of 15%. At 12 weeks after the last PDT treatment, 189 (79%) subjects in the Ameluz, and 154 (65%) in the Metvix group showed complete clearance.

For the NI testing, the lower-bound of the one-sided 97.5% confidence interval was greater than -15%, and the applicant concluded non-inferiority of Ameluz compared to Metvix (see Table 9 below); however, it should be noted that Metvix was not used at the approved U.S.-labeled dose. This was possibly because the trial was conducted ex-U.S, and Metvix may have been used according to the respective country's labeled dose. According to the FDA-approved label, Metvix was approved to be used with Aktilite CL128 lamp, and requires two PDTs, 1 week apart. In Trial 02, the PDT for Metvix included broadband (Waldmann, Hydrosun Photodyn lamps) as well as narrowband (Omnilux, Aktilite lamps) light sources, and those randomized to Metvix did not receive a 2nd PDT one week after the 1st PDT. Thus, with such differences in the lamp types and the number of PDT treatments, comparison of Ameluz against Metvix would not be appropriate. Further, as previously conveyed to the sponsor, for a comparative claim, generally two active-controlled Phase 3 trials would be required.

Table 9. Non-inferiority testing of BF200-ALA vs. Metvix(1) (Trial 02)

Trial 02			
Endpoint	Ameluz	Vehicle	Metvix(1)
12 weeks after the 1st PDT	120/248 (48%)	3/76 (4%)	91/246 (37%)
	Difference against (97.5% one-sided CI):	44% (37, 52)	11% (3, inf)

Source: applicant's table (11.2.1.1); (1) Withdrawn from the U.S. market (effective date: 11/12/2015).

3.2.3.1.2 Trials 03 and 07

For the analysis of the primary endpoint, the Ameluz was superior to vehicle using the protocol-specified analysis method of CMH test stratified by center and Fisher's Exact Test for Trials 03 and 07, respectively, on a 2-sided significance level of 0.05 (p-value< 0.0001). As with Trial 02, the complete clearance rate at Week 12 for those that used the narrowband PDT was higher than those that used the broadband PDT, and the response rates from those that received the 2nd PDT were similar to the response rate of the 1st PDT.

As with Trial 02, in Trials 03 and 07, the treatment effects from of the narrowband PDTs were higher than that of the broadband (Photodyn) PDT. The complete clearance rates at 12 weeks after the 1st PDT were similar to those after the 2nd PDT. Table 10 presents primary efficacy results for Trials 03 and 07.

Table 10. Complete clearance at 12 weeks after the last PDT by light source, lamp type, and PDT (Trials 03 and 07)

Trial 03				Trial 07		
		Ameluz N=81	Vehicle N=41		Ameluz N=55	Vehicle N=32
Complete Clearance		53 (65%)	5 (12%)	Complete Clearance	50/55 (91%)	7/32 (22%)
Light	Lamp			Light source		
Narrow	Aktilite	27/32 (84%)	2/16 (13%)	BF-RhodoLED	50/55 (91%)	7/32 (22%)
	1st PDT	22/32 (69%)	2/16 (13%)	*1st PDT*	34/55 (62%)	3/32 (9%)
	2nd PDT	5/10 (50%)	0/14 (0%)	*2nd PDT*	16/21 (76%)	4/29 (14%)
Broad	Photodyn	26/49 (53%)	3/25 (12%)			
	1st PDT	16/49 (33%)	2/25 (8%)			
	2nd PDT	10/33 (30%)	1/22 (5%)			

Source: reviewer table

3.4 Evaluation of Safety

This review only briefly discusses the treatment-emergent adverse events (TEAE) observed for the Phase 3 trials. For all three trials, the most common application site TEAEs included irritation, erythema, pain, oedema, pruritus, exfoliation, scab, induration, vesicles, etc. Refer to the clinical review for details. Tables 11 and 12 below present the application TEAE in Trials 02, 03, and 07.

Table 11. Application Site Treatment-Emergent Adverse Events (occurring ≥2%) in the safety analysis set (Trial 02)

Trial 02			
Treatment-Emergent Adverse Events (TEAE)	Ameluz N=248	Vehicle N=76	Metvix N=246[(1)]
Total with at least 1 TEAE	239 (96%)	55 (72%)	241 (98%)
Application Site Irritation	219 (88%)	25 (33%)	222 (90%)
Application Site Erythema	198 (80%)	31 (41%)	199 (81%)
Application Site Pain	175 (71%)	19 (25%)	179 (73%)
Application Site Oedema	62 (25%)	1 (1%)	61 (25%)
Application Site Pruritus	60 (24%)	6 (8%)	60 (24%)
Application Site Exfoliation	44 (18%)	5 (7%)	44 (18%)
Application Site Scab	27 (11%)	2 (3%)	30 (12%)
Application Site Induration	24 (10%)	0	21 (9%)
Application Site Vesicles	22 (9%)	1 (1%)	23 (9%)
Application Site Paraesthesia	17 (7%)	2 (3%)	18 (7%)
Application Site Hypersensitivity	10 (4%)	0	3 (1%)
Application Site Erosion	8% (3%)	1 (1%)	6 (2%)

Source: applicant's study report

Table 12. Application Site Treatment-Emergent Adverse Events (occurring ≥2%) in the safety analysis set (Trials 03 and 07)

	Trial 03		Trial 07	
	Ameluz N=81	Vehicle N=41	Ameluz N=55	Vehicle N=32
Subjects with any TEAE	78 (96%)	20 (49%)	55 (100%)	22 (69%)
Application Site Discomfort	1 (1%)	-	5 (9%)	0 (0%)
Application Site Erythema	72 (89%)	15 (37%)	51 (93%)	11 (34%)
Application Site Induration	12 (15%)	-	-	-
Application Site irritation	70 (86%)	10 (24%)	-	-
Application Site Edema	39 (40%)	1 (2%)	12 (22%)	1 (3%)
Application Site Pain	62 (54%)	4 (10%)	53 (98%)	16 (50%)
Application Site Pruritus	32 (33%)	-	21 (38%)	9 (28%)
Application Site Reaction	9 (11%)	2 (5%)	-	-
Application Site Scab	1 (1%)	-	20 (36%)	1 (3%)
Application Site Exfoliation	-	-	17 (31%)	1 (3%)

Source: applicant's study report

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, the efficacy by gender, age, baseline disease severity, and center for the Phase 3 trials were considered.

4.1 Efficacy by Gender, Age

Table 13 below shows the efficacy by gender, age groups at baseline by light source (narrow vs. broadband spectrum PDT). The majority of the subjects enrolled was male (86%), and of >65 of age (approximately 84%). Therefore, any differences in efficacy for the female subjects and ≤65 years of age subgroups would be difficult to detect. All subjects were white. Table 13 presents the complete clearance rate at 12 weeks after the last PDT by gender, and age subgroups by the respective light source (narrow vs. broad) for the PDT in Trial 02.

Table 13. Complete clearance at 12 weeks after the last PDT by gender, age groups (Trial 02)

Trial 02				
Light Source		Ameluz N=248	Vehicle N=76	Metvix N=246[(1)]
Complete Clearance at Week 12 after the last PDT		194 (78%)	13 (17%)	158 (64%)
Narrow		106/125 (85%)	5/39 (13%)	85/126 (67%)
Broad		88/123 (72%)	8/37 (22%)	73/119 (61%)
Light Source	Subgroup	Ameluz	Vehicle	Metvix
Narrow	Gender			
	Male	87/106 (82%)	5/29 (17%)	67/105 (64%)
	Female	19/19 (100%)	0/10 (0%)	18/21 (86%)
	Age Groups			
	≤65	26/29 (90%)	0/3 (0%)	21/27 (78%)
	>65	80/96 (83%)	5/36 (14%)	64/99 (65%)
Broad	Gender			
	Male	77/108 (71%)	8/31 (26%)	62/99 (63%)
	Female	11/15 (73%)	0/6 (0%)	11/20 (55%)
	Age Groups			
	≤65	22/26 (85%)	2/8 (25%)	16/21 (76%)
	>65	66/97 (68%)	6/29 (21%)	57/98 (58%)

Source: Reviewer's table; (1) Subject # 109/20 that received BF200ALA switched from Omnilux to Aktilite; Subject #109/10 that received Metvix switched from the Omnilux to the Waldmann lamp; ; as the subject switched from narrow to broad, this subject was neither classified as "narrow" nor "broad".

Table 14 presents the complete clearance rate at 12 weeks after the last PDT by gender, and age subgroups by the respective light source (narrow vs. broad) for the PDT in Trials 03 and 07.

Table 14. Complete clearance at 12 weeks after the last PDT by gender, age groups (Trials 03 and 07)

		Trial 03		Trial 07	
		Ameluz N=81	Vehicle N=41	Ameluz N=55	Vehicle N=32
Complete Clearance at Week 12 after the last PDT		53 (65%)	5 (12%)	50/55 (91%)	7/32 (22%)
	Narrow	27/32 (84%)	2/16 (13%)	50/55 (91%)	7/32 (22%)
	Broad	26/49 (53%)	3/25 (12%)	N/A	N/A
Narrow	Gender				
	Male	24/29 (83%)	1/13 (8%)	45/50 (90%)	7/29 (24%)
	Female	3/3 (100%)	1/3 (33%)	5/5 (100%)	0/3 (0%)
	Age				
	≤65	5/5 (100%)	0/4 (0%)	8/9 (89%)	6/26 (23%)
	>65	22/27 (81%)	2/12 (16%)	42/46 (91%)	1/6 (17%)
Broad	Gender			N/A	
	Male	23/44 (52%)	3/19 (16%)		
	Female	3/5 (60%)	0/6 (0%)		
	Age				
	≤65	4/7 (57%)	1/4 (25%)		
	>65	22/42 (52%)	2/21 (10%)		

Source: reviewer table

4.2 Efficacy by Baseline Disease Severity, Treatment Area

Efficacy by baseline disease severity in Table 15 show the majority of the subjects were of "moderate" AK severity based on the Olsen scale (1991), and of Fitzpatrick I-IV. Most subjects had the AK located on the face/forehead. Therefore, any differences in efficacy for the "mild" AK subjects and those with Fitzpatrick V or VI would be difficult to detect. Similar results were obtained for Trials 03 and 07 (Table 16). Table 15 also includes the efficacy results by location of AK (treatment area). The complete clearance rates by treatment area show that the treatment effect was higher in the face/forehead area compared to that of the scalp area; however, as the number of subjects is relatively small in the vehicle arm for the scalp, it will be difficult to draw conclusion regarding the differential treatment effect based on the treatment area.

Table 15. Efficacy by baseline disease severity and treatment area for Trial 02

Trial 02			
	Ameluz N=248	Vehicle N=76	Metvix N=246
AK severity			
Mild	33/39 (85%)	3/14 (21%)	38/41 (93%)
Moderate	161/209 (77%)	10/62 (16%)	120/205 (59%)
Fitzpatrick skin type			
I	2/3 (67%)	0/2 (0%)	3/6 (50%)
II	77/90 (86%)	4/27 (15%)	46/82 (56%)
III	85/118 (72%)	8/43 (19%)	92/133 (69%)
IV	30/35 (86%)	1/4 (25%)	16/23 (70%)
V, VI	0/2 (0%)	0	1/2 (50%)
Location of AK			
Treatment Area A (face/forehead)	122/149 (82%)	4/39 (10%)	107/138 (78%)
Treatment Area B (scalp)	47/67 (70%)	5/21 (24%)	23/58 (40%)
Both A and B	25/32 (78%)	4/16 (25%)	28/50 (56%)

Source: Reviewer table

As with Trial 02, any differences in efficacy for the "mild" AK subjects and those with Fitzpatrick V or VI would be difficult to detect. Similar results were obtained for Trials 03 and 07 (Table 16). Additionally, similar to the results of Trial 02, the complete clearance rates by treatment area in Trials 03 and 07 show that the treatment effect is higher in the face/forehead area compared to that of the scalp area. As with Trial 02, the number of subjects in the vehicle arm is small, therefore, it will be difficult to draw conclusion regarding the differential treatment effect based on the treatment area.

Table 16. Efficacy by baseline demographic characteristics for Trials 03 and 07

	Trial 03		Trial 07	
	Ameluz	Vehicle	Ameluz	Vehicle
ITT	81 (1)	41 (1)	55	32
AK severity				
Mild	15/20 (75%)	2/12 (17%)	11/11 (100%)	5/7 (71%)
Moderate	38/61 (62%)	3/29 (10%)	39/44 (89%)	2/25 (25%)
Fitzpatrick skin type				
I	3/5 (60%)	0/1 (0%)	1/1 (100%)	0
II	31/42 (74%)	2/29 (7%)	25/28 (89%)	6/12 (50%)
III	18/32 (56%)	3/11 (27%)	19/19 (100%)	1/19 (5%)
IV	1/2 (50%)	0	4/6 (67%)	0/1 (0%)
V, VI	0	0	1/1 (100%)	0
Location of AK				
Treatment Area A (face/forehead)	35/50 (70%)	2/26 (8%)	31/32 (97%)	6/17 (35%)
Treatment Area B (scalp)	13/22 (59%)	3/11 (27%)	18/22 (82%)	1/14 (7%)
Both A and B	5/9 (56%)	0/4 (0%)	1/1 (2%)	0/1 (0%)

Source: Reviewer table; (1) the applicant excluded 1 subject (ALA-AK-CT003/05-917) in Ameluz, and 1 subject (ALA-AK-CT003/06-908) in vehicle arm, because they did not receive post-baseline AK assessments after the first PDT. It should be noted that the above subjects were considered in the reviewer's ITT set for efficacy analyses.

4.3 Efficacy by Center

Tables 17 and 18 present the efficacy by center results for Trials 02, 03, and 07. Note that all three trials were conducted outside the U.S. For Trial 02 which randomized subjects in a 3:3:1 ratio to Ameluz: Metvix: Vehicle, respectively, the randomization was not stratified by center. Consequently, there were several centers that enrolled a small number of subjects in each arm with many centers with the vehicle arm enrolling 1 or 2 subjects. Given the number of subjects in the centers was relatively small, the findings from centers were expected to have large variability due to chance.

Table 17. Efficacy by center for each light source (Trial 02)

Trial 02				
Light Source	Site	Ameluz	Vehicle	Metvix
Broad	108	10/11 (91%)	1/3 (33%)	9/10 (90%)
	109	5/5 (100%)	0/1 (0%)	2/2 (100%)
	110	12/15 (80%)	2/4 (50%)	7/13 (54%)
	111	8/9 (89%)	0/2 (0%)	10/10 (100%)
	112	11/20 (55%)	1/7 (14%)	14/20 (70%)
	114	4/7 (57%)	1/2 (50%)	8/8 (100%)
	119	10/12 (83%)	3/4 (75%)	9/12 (75%)
	122	4/7 (57%)	0/1 (0%)	2/6 (33%)
	302	0/1 (0%)	-	0/1 (0%)
Narrow	102	3/3 (100%)	0/1 (0%)	2/4 (50%)
	103	5/5 (0%)	0/1 (0%)	4/5 (50%)
	105	10/10 (100%)	1/3 (33%)	7/9 (78%)
	106	1/1 (100%)	-	1/1 (100%)
	107	5/5 (100%)	0/1 (0%)	2/3 (67%)
	109	6/6 (100%)	0/1 (0%)	4/4 (100%)
	113	5/6 (83%)	0/2 (0%)	4/7 (57%)
	115	16/18 (89%)	1/5 (20%)	11/15 (73%)
	116	14/15 (93%)	2/5 (40%)	12/15 (80%)
	117	3/4 (75%)	0/2 (0%)	4/6 (67%)
	118	17/20 (85%)	0/6 (0%)	17/20 (85%)
	120	13/18 (72%)	1/7 (14%)	8/19 (42%)
	121	5/5 (100%)	0/2 (0%)	3/7 (43%)
	123	0/2 (0%)	0/1 (0%)	1/1 (100%)
	301	1/1 (100%)	0/1 (0%)	3/4 (75%)
	401	2/6 (33%)	0/1 (0%)	2/6 (33%)

Source: reviewer table

Table 18. Efficacy by center for each light source (Trials 03, 07)

	Trial 03			Trial 07		
Light Source	Site	Ameluz	Vehicle	Site	Ameluz	Vehicle
Broad	02	7/13 (54%)	0/7 (0%)	N/A		
	03	4/12 (33%)	1/6 (17%)			
	04	8/12 (67%)	1/6 (17%)			
	07	7/12 (58%)	1/6 (17%)			
Narrow	01	8/9 (89%)	1/4 (25%)	01	10/11 (91%)	2/6 (33%)
	05	11/11 (100%)	0/6 (0%)	02	8/8 (100%)	0/4 (0%)
	06	2/5 (40%)	0/2 (0%)	03	3/5 (60%)	0/4 (0%)
	08	6/6 (100%)	1/3 (33%)	04	10/12 (83%)	0/6 (0%)
				05	11/11 (100%)	2/5 (40%)
				06	4/4 (100%)	0/4 (0%)
				07	4/4 (100%)	3/3 (100%)

Source: reviewer table

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For Trial 02, the applicant compared Ameluz to Metvix using non-inferiority (NI) testing with the NI margin of 15%. As the lower-bound of the one-sided 97.5% confidence interval was greater than -15%, and the applicant concluded non-inferiority of Ameluz compared to Metvix; however, Metvix was not used at the approved U.S.-labeled dose. According to the FDA-approved label, Metvix was approved to be used with Aktilite CL128 lamp, and requires two PDTs, 1 week apart. In Trial 02, the PDT for Metvix included broadband (Waldmann, Hydrosun Photodyn lamps) as well as narrowband (Omnilux, Aktilite lamps) light sources, and those randomized to Metvix did not receive a 2nd PDT one week after the 1st PDT. Thus, with such differences in the lamp types and the number of PDT treatments, comparison of Ameluz against Metvix would not be appropriate. Further, as previously conveyed to the sponsor, for a comparative claim, generally two active-controlled Phase 3 trials would be required. Consequently, any findings from such comparison would be exploratory at best.

Each Phase 3 trial listed several secondary endpoints including the proportion of subjects or AK lesions with complete clearance after each assessment, partial response assessed 12 weeks after the last PDT, overall cosmetic outcome after the last PDT, among other endpoints. However, for the analysis of the secondary endpoints, the list and the order of the secondary endpoints across the three Phase 3 trials were different, and given the lack of plan for multiplicity adjustment to control the Type I error rate in Trials 02 and 03, there was no replication of study findings for secondary endpoints from the three Phase 3 trials.

5.2 Conclusions and Recommendations

Ameluz® gel was superior to vehicle gel in the treatment of **mild to moderate** actinic keratosis (AK) on the face and/or scalp in three Phase 3 trials, ALA-AK-CT002, ALA-AK-CT003, and ALA-AK-CT007 (from hereon denoted as Trials 02, 03, and 07). The trials enrolled male or female subjects between 18 and 85 years of age (inclusive), with 4-8 clinically confirmed AK target lesions of mild to moderate intensity within the face or bald scalp excluding eyes, nostrils, ears and mouth, (i.e., AK grade I or II according to Olsen *et al*., 1991) at baseline.

The protocol-specified primary efficacy endpoint for all three trials was the overall patient complete response assessed 12 weeks after the last photodynamic therapy (PDT), and an overall complete responder was defined as a patient, in whom all treated lesions were cleared, including patients receiving the second treatment, if necessary. Efficacy results for the primary endpoint were statistically significant for all three trials (p-value< 0.0001). As Trials 02 and 03 used PDTs from both narrowband as well as broadband spectrum light sources, Table 1 presents the efficacy results for the primary endpoint, the

overall patient complete response assessed 12 weeks after the last PDT, and the efficacy results by the light source (i.e., narrow vs. broad) as well.

Table 1. Proportion of subjects achieving Complete Clearance 12 weeks after the last photodynamic therapy (PDT)

Trial 02			
	BF200ALA N=248	Vehicle N=76	Metvix N=246
Complete Clearance	194 (78%)	13 (17%)	158 (64%)
p-value	< 0.0001[1]		N/A
By light source			
Narrow	106/125 (85%)	5/39 (13%)	85/126 (67%)
Broad	88/123 (72%)	8/37 (22%)	73/119 (61%)

	Trial 03		Trial 07	
Light Source	BF200ALA N=81	Vehicle N=41	BF200ALA N=55	Vehicle N=32
Complete Clearance	53 (65%)	5 (12%)	50/55 (91%)	7/32 (22%)
p-value	< 0.0001[2]		< 0.0001 [3]	
By light source				
Narrow	27/32 (84%)	2/16 (13%)	50/55 (91%)	7/32 (22%)
Broad	26/49 (53%)	3/25 (12%)	N/A	

Source: reviewer's table; (1) p-value from Chi-square test; (2) p-value from CMH test stratified by center; (3) p-value from Fisher's Exact Test. The primary imputation method was the last observation carried forward (LOCF).

6. Appendix

Per the clinical team's request, the subject disposition tables for all three Phase 3 trials of subjects that were treated only with the narrowband PDTs are presented below.

6.1 Subject Disposition Tables for Those Receiving Narrowband PDT only

Of the subjects treated with the narrowband PDTs, for Trial 02, a total of 5 (4%) Ameluz-treated subjects, 5 (13%) vehicle-treated subjects, and 4 (3%) Metvix-treated subjects discontinued the trial. Subject disposition table for the subjects that received narrowband PDT in Trials 02 is presented in Table A.1.

Table A.1. Subject Disposition for Trial 02 (Narrowband PDT only)

Trial 02			
Narrowband PDT	Ameluz N=125	Vehicle N=39	Metvix N=126
Discontinued	5 (4%)	5 (13%)	4 (3%)
Reasons for discontinuation			
Subject's decision	4	2	2
AE	1	0	0
Lack of efficacy	0	2	0
Lost to follow-up	0	0	0
Protocol violation	0	0	1
Other	0	1	1

Source: Applicant's table; (1) Subject 115/10 did not receive PDT

Of the subjects treated with the narrowband PDTs, for Trial 03, a total of 4 (13%) Ameluz-treated subjects, and 3 (19%) vehicle-treated subjects discontinued the trial. According to the applicant's Appendix 16.2.1.1, the four vehicle-treated subjects that withdrew experienced lack of efficacy. For Trial 07, all subjects received the narrowband BF-RhodoLED lamp. Subject disposition for subjects with narrowband PDTs for Trial 03 is in Table A.2.

Table A.2. Subject Disposition for Trial 03 (Narrowband PDT only)

Trial 03		
Narrowband PDT	Ameluz N=32	Vehicle N=16
Discontinued	4 (13%)	3 (19%)
Reasons for discontinuation		
Protocol deviation	1	0
Adverse Event	0	0
Lack of tolerability	0	0
Loss to follow-up	0	0
Other	3	3 (1)
Patient's decision	0	0

Source: Applicant's table; (1) Appendix 16.2.1.1 specified that these subjects had "insufficient outcome of treatment", or "therapy not successful".

6.2 Baseline Demographics for Those Receiving Narrowband PDT only

Of the subjects treated with the narrowband PDTs, as with the demographics tables from the overall ITT population (Tables 6 and 7), the baseline demographics were generally balanced across the treatment arms for those treated with narrowband PDTs.

For all three trials, the majority of the subjects were male (approximately 86%) and all subjects were Caucasian in all three trials. The mean age of subjects was approximately 70 years (range 49 years to 87 years). Most subjects were of Fitzpatrick skin type I, II or III (91%), and the majority of subjects (74%) had the AK on the face and/or forehead. The baseline demographics of subjects that received the narrowband PDTs in Trial 02 and 03 are presented in Tables A.3 and A.4 below.

Table A.3. Baseline demographic characteristics of subjects that received narrowband PDTs for Trial 02

Trial 02			
Narrowband PDT	Ameluz N=125	Vehicle N=39	Metvix N=126
Age			
mean ± SD	70.0 ± 7.0	72.6 ± 6.0	71.7 ± 7.6
Range	49, 87	64, 84	44, 85
Gender			
Male	106 (85%)	29 (74%)	105 (83%)
Female	19 (15%)	10 (26%)	21 (17%)
Fitzpatrick skin type			
I	3 (2%)	1 (3%)	3 (2%)
II	40 (32%)	16 (41%)	40 (32%)
III	68 (54%)	20 (51%)	71 (56%)
IV	14 (11%)	2 (5%)	10 (8%)
V	0 (0%)	0 (0%)	2 (2%)
Location of AK			
Treatment Area A (face/forehead)	73 (58%)	22 (56%)	76 (60%)
Treatment Area B (bald scalp)	31 (25%)	11 (28%)	26 (21%)
Both A and B	21 (17%)	6 (15%)	24 (19%)

Source: Reviewer table

Table A.4. Baseline demographic characteristics of subjects that received narrowband PDTs for Trials 03 and 07

Trial 03			Trial 07	
Narrowband PDT	Ameluz N=32	Vehicle N=16	Ameluz N=55	Vehicle N=32
Age				
mean ± SD	69.8 ± 4.8	69.6 ± 7.7	71.9 ± 6.4	71.0 ± 6.4
Range	60, 80	57, 85	56, 84	51, 84
Gender				
Male	29 (91%)	13 (81%)	50 (91%)	29 (91%)
Female	3 (9%)	3 (19%)	5 (9%)	3 (9%)
Fitzpatrick skin type				
I	1 (3%)	0 (0%)	1 (2%)	-
II	22 (69%)	11 (69%)	28 (51%)	12 (38%)
III	8 (25%)	5 (32%)	19 (35%)	19 (59%)
IV	1 (3%)	0 (0%)	6 (11%)	1 (3%)
V	0 (0%)	0 (0%)	1 (2%)	-
Location of AK				
Treatment Area A (face/forehead)	23 (72%)	12 (75%)	32 (58%)	17 (53%)
Treatment Area B (scalp)	5 (16%)	3 (19%)	22 (40%)	14 (44%)
Both A and B	4 (13%)	1 (6%)	1 (2%)	1 (3%)

Source: Reviewer table

6.3 Recurrence Rates at Months 6 and 12 for those that received narrowband PDTs

Subjects who achieved complete clearance 12 weeks after the last PDT entered a12-month follow-up period. In Trials 02, 03, and 07, the subjects that received Ameluz with the narrowband PDTs and achieved complete clearance 12 weeks after the last PDT, had recurrence rates of 14%, 11%, 25% (at 6 months) and 40%, 22%, and 37% (at 12 months), respectively. Recurrence was defined as the percentage of subjects with at least one recurrent lesion during follow up period in subjects with completely cleared lesions 12 weeks after the last PDT. Table A.5 presents the recurrence rates at Months 6 and 12 after the last PDT in Trials 02, 03, and 07.

Table A.5 presents the Recurrence Rates at Months 6 and 12 after the last PDT in Trials 02, 03, and 07.

Narrowband PDT	Length of Follow-up	Ameluz	Vehicle	Metvix
Trial 02	6 months	14/101 (14%)	1/5 (20%)	11/81 (14%)
	12 months	39/98[(1)] (40%)	2/5 (40%)	33/81 (41%)
Trial 03	6 months	3/27 (11%)	-	
	12 months	6/27 (22%)	-	
Trial 07	6 months	12/49 (25%)	1/7 (14%)	
	12 months	18/49 (37%)	1/7 (14%)	

Source: applicant's tables; (1) 3 subjects were lost to follow-up.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARIN J KIM
03/09/2016

MOHAMED A ALOSH
03/09/2016