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Long-term (6 and 12 months) follow-up of two prospective, randomized, controlled phase III trials of photodynamic therapy with BF-200 ALA and MAL for the treatment of actinic keratosis

Authors

The AK-CT002 and AK-CT003 Study Groups:

T. Dirschka (1), P. Radny (2), R. Dominicus (3), H. Mensing (4), H. Brüning (5), L. Jenne (6), L. Karl (7), M. Sebastian (8), C. Oster-Schmidt (9), W. Klövekorn (10), U. Reinhold (11), M. Tanner (12), D. Gröne (13), M. Deichmann (14), M. Simon (15), F. Hübinger (16), G. Hofbauer (17), G. Krähn-Senftleben (18), F. Borrosch (19), K. Reich (20), C. Berking (21), P. Wolf (22), P. Lehmann (23), M. Moers-Carpi (24), H. Hönigsmann (25), K. Wernicke-Panten (26), S. Hahn (26), G. Pabst (27), D. Voss (27), M. Foguet (28), B. Schmitz (28), H. Lübbert (28), R.-M. Szeimies (29)

1) *Private Dermatological Practice Centre, Wuppertal, Germany and Faculty of Health, University Witten-Herdecke, Witten, Germany;*
2) *Private Dermatological Practice, Friedrichshafen, Germany;*
3) *Private Practice Dres.Joachim Bockhorst und Rolf Dominicus, Dülmen, Germany;*
4) *Dermatological Ambulatory, Hamburg, Germany:*
5) *Day Hospital for Allergy and Skin Diseases, Kiel, Germany;*
6) *Private Practice im Sellspeicher, Kiel, Germany;*
7) *Dermatological Practice, Soest, Germany;*
8) *Private Practice Mahlow, Germany;*
9) *Private Practice for Skin and Genital Diseases Altenkirchen, Altenkirchen, Germany;*
10) *Private Dermatological Practice, Gilching, Germany;*
11) *Medical Centre Bonn, Bonn, Germany;*
12) *Dermatosurgery Center Noerdlingen, Nördlingen, Germany;*
13) *Dermatological Practice, Berlin, Germany;*
14) *Dermatological Practice , Gelnhausen, Germany;*
15) *Dermatological Practice, Clinical Study Centre, Berlin, Germany;*
16) *Private Practice, Wuppertal, Germany;*
17) *University Hospital Zurich, Clinic of Dermatology, Zurich, Switzerland;*
18) *Cutis Sana Dermatologists, Blaubeuren, Germany;*
19) *Centre for Dermatology Vechta, Vechta, Germany;*
20) *SCIderm GmbH, Hamburg, Germany;*
21) *Clinic for Dermatology und Allergology, Ludwig-Maximilian-University Munich, Munich, Germany;*
22) *Department of Dermatology and Venereology, Research Unit forPhotodermatology, Medical University of Graz, Graz, Austria;*
23) *HELIOS Hospital Wuppertal, Wuppertal, Germany;*
24) *Private Practice for Skin Diseases, Operative & Aesthetical Dermatology, Munich, Germany;*
25) *University Hospital for Dermatology, Wien, Austria;*
26) *Accovion GmbH, Eschborn, Germany;*

27) Focus Clinical Drug Development GmbH, Neuss, German;
28) Biofrontera Bioscience GmbH, Leverkusen, Germany;
29) Klinikum Vest, Dept. of Dermatology and Allergology, Recklinghausen, Germany

Correspondence

Dr. Beate Schmitz

Biofrontera Bioscience GmbH
Hemmelrather Weg 201
D-51377 Leverkusen
Tel. +49 (214) 876 32 41
Fax. +49 (214) 876 32 90
b.schmitz@biofrontera.com

Topics

- BF-200 ALA is a stable nanoemulsion-based gel formulation of ALA for PDT of AK which demonstrated significantly higher efficacy compared to a registered MAL cream.
- 6- and 12-month follow-up results of two pivotal phase III studies with BF-200 ALA for PDT of AK in comparison to placebo and a registered MAL cream.
- Comparison of recurrence rates after using different light sources for PDT of AK.

Key words

actinic keratosis, aminolaevulinic acid, photodynamic therapy, multicentre trials, randomized controlled trial, phase III, methyl-aminolaevulinic acid, follow-up

Conflicts of interest

T.D. and R.-M.S. are consultants of the sponsoring company. K.WP., S.H., G.P. and D.V. are employees of the company responsible for data management and statistical analyses. M.F., B.S. and H.L. are employees of the sponsoring company.

Abstract

Background

Two phase III trials of photodynamic therapy (PDT) with BF-200 ALA, a recently approved nanoemulsion formulation of 5-aminolaevulinic acid (ALA) demonstrated high clearance rates in mild to moderate actinic keratosis (AK). The comparison to a registered methyl–ALA (MAL) cream demonstrated significantly superior total patient clearance rates.

Objectives

To evaluate long-term efficacy and safety of PDT for AK 6 and 12 months after the last PDT with BF-200 ALA, MAL or placebo.

Patients/Methods

The follow-up phase (FUP) was performed with patients of two phase III studies. Both studies compared BF-200 ALA with placebo, one of the studies additionally with MAL. Overall recurrence rates and various subgroups (light source, lesion severity, lesion location, complete responders after 1st PDT) were assessed 6 and 12 months after the last PDT.

Results

Recurrence rates were similar for BF-200 ALA and MAL, with a tendency to lower recurrence rates for BF-200 ALA. The proportion of patients who were fully cleared during PDT and remained completely cleared for at least12 months after PDT were 47% for BF-200 ALA (both studies) and 36% for MAL treatment. The subgroup that was illuminated with narrow wavelength LED lamps reached 69% and 53% for BF-200 ALA (both studies, respectively) and 41% for MAL. No safety concerns were reported.

Conclusions

The FUP data confirmed the high efficacy and safety of PDT with BF-200 ALA. The slightly lower recurrence rates after BF-200 ALA treatment compared to MAL treatment enhanced the better treatment outcome due to the significantly superior efficacy.

Introduction

Actinic keratosis is defined as squamous cell carcinoma in situ[1;2]. It represents the most common neoplasia affecting fair-skinned subjects in sun-exposed body areas like face and scalp. AKs may progress to squamous cell carcinoma, therefore necessitating treatment[3;4]. Since photodynamic therapy (PDT) with 5-aminolaevulinic acid (ALA) or its derivative methyl-aminolaevulinate (MAL) combines high efficacy with an excellent cosmetic outcome, it is recommended as one of the first line treatments in this indication[1].

Extemporal formulations containing ALA have frequently been used clinically, but are often restrained by their short-term stability and poor skin penetration. BF-200 ALA is a new nanoemulsion-based gel formulation containing 7.8% ALA (10% ALA hydrochloride), which overcomes these drawbacks, displaying an improved stability of ALA in the aqueous formulation and an enhanced penetration into the epidermis[5]. Based on these advantages,

lower ALA concentrations are sufficient for an excellent therapeutic outcome, which was recently demonstrated in two phase III studies of the treatment of actinic keratosis, one of them in comparison to a registered MAL formulation[6;7].

Here we present the recurrence rates of subjects treated with BF-200 ALA or MAL PDT in two phase III trials and the percentage of patients who were totally cleared of AK 12-months after PDT. Safety issues such as new lesions and skin cancer in the treatment area are also reported.

Material and Methods

Data were collected during the follow-up period (FUP) of two randomized, placebo-controlled, multicentre phase III clinical studies[6;7]. All subjects in both studies entered the FUP three months after the last treatment and were invited to two FUP visits, the first at 6 and the second at 12 months after the last PDT. Patient assessments at the FUP visits were analyzed distinct from the study and summarized in a separate report. The studies were approved by the responsible ethics committees and the competent authorities (BfArM, Germany; Swissmedic, Switzerland; BASG, Austria) and performed according to the National Drug Laws, the guidelines of Good Clinical Practice and the Declaration of Helsinki.

During the clinical part of the studies, eligible subjects with 4-8 mild to moderate AK lesions (Olsen grade I or II[8]) on the face or scalp were treated with either BF-200 ALA containing 78 mg/g ALA (now registered as Ameluz®, Biofrontera, Germany), a registered MAL cream (Metvix®, Galderma, Germany) containing 160 mg/g of MAL, or placebo matching the BF-200 ALA formulation. After roughening of lesion surfaces and cleaning the skin with alcohol, medications were applied for 3 hours. Then, remnant gel or cream were carefully wiped off and lesions were illuminated with red light either with narrow spectrum lamps (LED lamps: Aktilite® CL 128, Omnilux PDT™) or broad spectrum light sources (PhotoDyn® 750/505, Waldmann® PDT 1200L) as described in detail in the study protocols[6;7]. Treatment efficacy and cosmetic outcome were assessed 3 months after PDT. In case of remaining lesions, a second treatment was performed at this time point. The final assessment was then carried out after 3 more months.

Study population

All subjects who completed the clinical trials and did not withdraw their informed consent were enrolled in the FUP to assess long-term treatment effects with respect to recurrences of AK lesions and safety issues. All subjects with complete remission of AK lesions in the treatment areas were included into the subjects-based recurrence analysis. Further, the design of the FUP of study ALA-AK-CT003 (superiority study over placebo[6]) allowed, in addition to following completely cleared patients, to follow every individual lesion that was completely cleared after the last PDT. This lesion-based FUP analysis was not performed in study ALA-AK-CT002 (comparative study to the registered MAL cream)[7] since only lesions of complete responders were considered in this trial.

Study Plan

To analyze patient and lesion long-term efficacy, patient visits to the study centers were scheduled 6 and 12 months after the last PDT (Fig 1). If recurrent lesions occurred, patients received an additional AK therapy chosen by the investigator. In addition to recurrent lesions, new AK lesions, skin cancers and cosmetic outcome in the treatment areas were recorded at the scheduled visits. Serious adverse events (SAEs) were recorded for both studies.

Recurrence rate assessment

Patients that were completely cleared at the end of the clinical study, i.e. 3 months after the last PDT, were included into the analysis. Patients or lesions completely cleared 3 months after the last PDT, but then diagnosed and/or treated at or before FUP visit 1 (i.e. 6 months after the last PDT) or FUP visit 2 (i.e. 12 months after the last PDT) were assessed as recurrent. In study ALA-AK-CT003, all totally cleared lesions were examined individually, both in patients with all lesions cleared and those with lesions remaining. Following each individual lesion was not done in study ALA-AK-CT002 (comparative study), where only complete responders were considered during FUP. The consequence of this is that if a subject in study ALA-AK-CT002 received any AK-therapy between the end of the clinical phase and FUP visit 2, or if a subject was flagged as recurrent, but the number of recurrent AKs was not recorded, all of the subjects' lesions were defined as recurrent. This leads to an overestimation of lesion-based recurrence rates in study ALA-AK-CT002.

If a patient was recurrent at FUP visit 1 he was also counted as recurrent at FUP visit 2, irrespective of an AK-therapy that may have cleared the patient in the meantime.

Non-recurrence rates were evaluated using the life-table method for grouped data. Two values were calculated: a) the probability that a patient or lesion, completely cleared at the end of the clinical phase of the study, remains completely cleared up to the 6- and 12-month FUP visit (p_i for visit i, i=1, 2), and b) the probability that a patient or lesion is fully cleared during PDT and remains completely cleared until the follow-up visit at 6 or 12 months after the last PDT (p_i*CR_P or p_i*CR_L; see below).

Biometric analysis

Data were obtained independently for both studies and reported for the intent to treat (ITT, ALA-AK-CT002) or the full analysis set (FAS, ALA-AK-CT003) population, respectively. Patient-based and lesion-based recurrence rates were estimated at both follow-up visits, i.e. after 6 months (FUP visit 1) and after 12 months (FUP visit 2), based on an approach of time to event analysis. As only two time points were considered the life-table method for grouped data was chosen. This is the grouped data equivalent to the Kaplan-Meier estimator. To adequately take withdrawals or lost to follow up patients into account it is assumed that the withdrawal times are continuously uniformly distributed on the time interval between the visits. This allows censoring half of the drop-outs at the beginning of the interval and the other half at the end of the interval. Table 1 shows how the estimators for subject based recurrence rates have been calculated.

Recurrence rates were assessed for treatment groups and various subgroups (e.g. by centre, gender, age, skin type, target area, light spectrum and AK severity at baseline if appropriate).

The approaches were performed taking into consideration (a) the number of subjects or lesions completely cleared at the end-of-study visit 3 months after the last PDT, (b) the number of subjects/lesions with complete remission in the target area(s) at the current visit, (c) the number of subjects with at least one recurrent lesion or new recurrent lesions in the target area(s) between the preceding and the current visit, (d) the number of subjects/lesions lost to follow-up or withdrawn between the preceding and the current visit.

For the FUP period, probabilities (p_i) for subjects to remain fully cleared up to the respective visit (visit i, i=1, 2) were assessed according to life-table estimates as shown in Table 1 (probabilities regarding totally cleared lesions were performed similarly).

First, the number of subjects with complete clearance of all AK lesions in the target area(s) at the current visit (CR_{Pi}) was calculated by subtracting subjects with at least one recurrent lesion in the target area(s) between the preceding and the current visit (R_i), and the number of subjects lost to follow-up or withdrawn between the preceding and the current visit (L_i) from the totally cleared patient group at the last visit (CR_{Pi-1}):

$$CR_{Pi} = CR_{P(i-1)} - R_i - L_i.$$

Second, for subjects with complete remission at the preceding visit, the probability of remaining cleared could then be calculated:

$$f_i = 1 - R_i/(CR_{Pi} - L_i/2).$$

Finally, the probability of remaining cleared up to the current visit could be estimated using the formula:

$$p_i = p_{(i-1)} * f_i$$

Furthermore, the probability that a patient or lesion, respectively, is cleared during treatment and remains cleared up to the current visit was estimated by multiplying the p_i of the assessed treatment group and the corresponding patient-based (CR_{P0}) or lesion-based clearance rate (CR_{L0}) 3 months after the last PDT (end of clinical trial); this term is defined as p_i*CR_P or $p_i*CR_{L,}$ respectively:

$$p_i*CR_P = p_i * CR_{P0}$$

Example for p_i*CR_P calculation: The p_1 value of 0.827 achieved at the FUP visit 1 for BF-200 ALA treated patients in the ALA-AK-CT003 study indicates that 82.7% of the patients who were completely cleared 3 months after the last PDT (66.3%) remain completely cleared at this time point. In addition, the corresponding product p_1*CR_P (0.827 * 0.663) of 0.548 takes the respective efficacy 3 months after the last PDT into consideration and reflects the probability of a patient entering PDT to be cleared at FUP visit 1 (for values see Tables 2A, 3A).

For the calculation of pi*CR data for comparator compounds, the required data were obtained from publications of controlled, randomized phase III trials[9;10;11;12]. The following values were taken from those references and entered the calculation: Number of completely cleared

patients at the end of the study, patients entering follow-up, patients lost to follow-up (wherever data are provided, otherwise set to 0), number of patients with at least one recurrent lesion during follow-up. Calculation was as described above and illustrated in Table 1.

New lesions or skin cancers observed in the target area were assessed by descriptive statistics.

Results

Patients

663 patients from both phase III studies entered the follow-up phase, accounting to 93.4% (114 patients) and 96.1% (549 patients) of the randomized subjects of studies ALA-AK-CT003 and ALA-AK-CT002, respectively. Of these, 63.3% (420 patients) were complete responders. 630 subjects completed the follow-up (102 subjects in study ALA-AK-CT003, 528 subjects in study ALA-AK-CT002) while 33 patients discontinued prematurely.

A flow chart of the patient disposition is presented in Fig. 2. Patient characteristics are summarized in Table 2. Results are shown for the ITT/FAS follow-up population.

Efficacy

Patient Non-Recurrence Rates

Rates of non-recurrent patients in the FUP of both pivotal studies are summarized in Table 3A (for study ALA-AK-CT003) and Table 3B (for study ALA-AK-CT002). No significant differences became apparent between BF-200 ALA and MAL-treated subjects at FUP visit 1. More than 80% of the patients were still complete responders 6 months after the last PDT with BF-200 ALA (in both studies) or MAL.

A slightly larger variation was observed at FUP visit 2 after 12 months, when for BF-200 ALA patients 58.4% in study ALA-AK-CT002 and 69.4% in ALA-AK-CT003 were still non-recurrent. For MAL, 55.2% of the patients were still completely cleared. The difference at FUP visit 2 between the patient clearance rates in the BF-200 ALA groups of the two pivotal trials may be partly due to the larger percentage of patients with moderate lesions (Olsen grade II) in study ALA-AK-CT002 (Table 2). In both studies, at FUP2 recurrence rates for Olsen grade II patients treated with BF-200 ALA were about 14 percentage points higher than for patients with only mild (Olsen Grade I) lesions (compare Table 5).

In study ALA-AK-CT002, the probability (p_2) in the BF-200 ALA group to remain cleared 12 months after the last PDT was 0.592, that for the MAL group 0.555. In study CT003 the probability to remain completely cleared after BF-200 ALA treatment at 12 months FUP was 0.706 (Table 3).

Combining efficacy and recurrence rates, the probability to be totally cleared 12 months after the last treatment (p_2*CR_{P0}) was 0.472 and 0.468 (ALA-AK-CT002 and ALA-AK-CT003, respectively) for BF-200 ALA patients, and 0.363 for MAL patients (ALA-AK-CT002; Table 3). In spite of the lower recurrence rate in study ALA-AK-CT003, the overall p_2*CR_P for BF-200 ALA were very similar in studies ALA-AK-CT003 and ALA-AK-CT002. This apparent discrepancy is due to the higher proportion of patients treated with broad spectrum lamps in

study ALA-AK-CT003, causing a lower overall efficacy (78.2% vs. 66.3% for CT002 and CT003, respectively; see Table 2A).

Since only fully cleared patients were considered for FUP, this generates a very small group of placebo patients. In addition, placebo patients presenting with all lesions totally cleared may represent a specific selection of patients with a strong ability for AK clearance. Thus, recurrence rates in the placebo groups can hardly be interpreted.

Lesion Recurrence Rate

1359 (90.4%) and 369 (81.1%) of BF-200 ALA treated lesions were totally cleared at the end of the clinical parts of studies ALA-AK-CT002 and ALA-AK-CT003, respectively, and 1295 (83.2%) of MAL-treated lesions in study ALA-AK-CT002 (Table 2). For the placebo groups, 182 (37.1%) and 46 (20.9%) of the lesions were cleared 12 weeks after the last treatment in the respective studies. 1147 and 353 of BF-200 ALA treated lesions, and 958 of MAL treated lesions entered the follow-up phase. 84 and 45 lesions were monitored in the respective placebo groups (Table 2). In contrast to study ALA-AK-CT003 in which every individual lesion was monitored during FUP, in study ALA-AK-CT002 only lesions of complete responders entered the FUP phase, reducing the total number of completely cleared lesions analyzed. This again leads to a small number of lesions followed up in the placebo group, rendering any interpretation of the results in this group questionable.

In the ALA-AK-CT002 study the overall lesion recurrence rates after 6 months were 7.0% for BF-200 ALA patients and 6.6% for MAL patients; 3.6% were recurrent in the placebo group. Lesion recurrence in ALA patients at FUP visit 1 in ALA-AK-CT003 was 7.4% and 6.1% for placebo patients. After 12 months, adding recurrence rates of FUP visit 1 and FUP visit 2, BF-200 ALA patients in study ALA-AK-CT002 had a lesion recurrence rate of 21.7%, MAL patients of 25.4% and placebo patients of 15%. In study ALA-AK-CT003, the combined lesion recurrence rates after 12 months were 16.7% for BF-200 ALA and 12.6% for placebo patients, respectively (Table 4).

The probabilities of lesions to remain totally cleared up to FUP visit 1 were very similar for BF-200 ALA and MAL patients with values around 0.93. Again, there were slight advantages for BF-200 ALA at FUP visit 2 with a p_2 of 0.855 for BF-200 ALA treated patients in study ALA-AK-CT002 versus 0.813 for MAL-treated patients. In the ALA-AK-CT003 study the corresponding probability was 0.843 (Table 4).

The differences in the lesion recurrence rates between the two pivotal studies are likely to be caused by the different way of counting recurrent lesions. While all lesions were recorded individually in study ALA-AK-CT003, all lesions of a patient were counted as recurrent in study ALA-AK-CT002 if this patient received any AK-therapy in between the scheduled visits or if the number of recurrent lesions was not recorded by the investigator. After 12 months (FUP2 of ALA-AK-CT002), 78 out of 127 recurrent lesions in the BF-200 ALA group, 104 out of 140 recurrent lesions in the MAL group and 8 out of 8 lesions in the placebo group belonged to the aforementioned patients. These high proportions illustrate that the procedure leads to an overestimation of lesion recurrence in the ALA-AK-CT002 study. It should not, however, affect any differences between lesion recurrence in the BF-200 ALA and MAL groups.

The probability to reach total lesion clearance 12 months after the last PDT (p_2*CR_L) was for BF-200 ALA 0.525 in ALA-AK-CT002 and 0.684 in ALA-AK-CT003, respectively. For

MAL the probability was 0.401, considerably lower than the probabilities with BF-200 ALA (Table 4).

Subgroups

In both pivotal studies a difference in the number of subjects with recurrent AK lesions treated either with narrow or broad spectrum light sources was obtained at both FUP visits for all verum groups (Table 5).

In the comparative study ALA-AK-CT002 a similar number of patients were still completely cleared 12 months after the last treatment with BF-200 ALA or MAL and illumination with LED devices (60.2% with BF-200 ALA and 59.3% with MAL, respectively). With broad spectrum devices this clearance rate was, with 56.3%, slightly lower for BF-200 ALA, while MAL showed a clearly reduced rate of 50.7% (Table 5). In study ALA-AK-CT003 a strong difference was observed between narrow and broad light spectrum lamps, with 76.9% and 60.9% of the BF-200 ALA patients remaining completely cleared, respectively (Table 5).

At FUP visit 2 after 12 months, the probabilities for lesions to remain totally cleared after treatment with LED lamps were 0.932 and 0.839 for BF-200 ALA (studies ALA-AK-CT003 and ALA-AK-CT002, respectively) and 0.813 for MAL (Table 4).

The analysis of the various subgroups shown in Table 5 showed that the recurrence rates after BF-200 ALA treatment compared to MAL treatment were in no case dramatically different. However, after 12 months FUP slightly lower recurrences were observed in all analyzed subgroups of BF-200 ALA treated patients, leading to the conclusion that there was a general tendency to slightly lower recurrence rates with this product (Table 5).

Mostly due to the significantly higher efficacy of BF-200 ALA, the probability for a patient to be totally cleared from all lesions after 12 months FUP (p_2*CR_P) was to the advantage of BF-200 ALA compared to MAL in all subgroups analysed (Table 5).

Cosmetic outcome

The cosmetic outcome was assessed by the investigator at 6 months FUP as very good or good in 39.7% and 43.1% subjects in the BF-200 ALA groups (study ALA-AK-CT002 and ALA-AK-CT003, respectively), in 42.6% of subjects in the MAL group (study ALA-AK-CT002), and 34.8% and 44.1% of subjects in the placebo groups (studies ALA-AK-CT002 and ALA-AK-CT003, respectively). An unsatisfactory or impaired assessment was obtained in 14.3% and 7.0% of subjects treated with BF-200 ALA (ALA-AK-CT002 and ALA-AK-CT003, respectively), and in 9.0% of MAL treated patients. Higher values were obtained for placebo with 13.7% and 20.6% in the respective studies.

At 12 months FUP, the cosmetic outcome was judged as very good or good in 38.9% and 45.0% of subjects in the BF-200 ALA groups (ALA-AK-CT002 and ALA-AK-CT003, respectively), in 41.1% of subjects in the MAL group, and in 32.8% and 46.9% of subjects in the placebo groups (ALA-AK-CT002 and ALA-AK-CT003, respectively). Unsatisfactory or impaired outcome was reported to a similar extent in all groups (15.0% and 14.1% of BF-200 ALA treated patients, 16.5% of MAL-treated subjects, 15.7% and 18.8% of placebo patients, respectively).

Safety and Tolerability

Sixty-one AEs were reported during the FUP of study ALA-AK-CT002 which occurred to a similar extent in the three study arms (11.6%, 11.3% and 8.8% in the BF-200 ALA, the MAL, and the placebo groups, respectively). All events were classified as unrelated with the exception of one subject with squamous cell carcinoma (SCC) in the BF-200 ALA group, two patients with basal cell carcinomas (BCC) in the MAL group and one subject each with Bowen's disease in the MAL and placebo groups. No AEs were assessed in the ALA-AK-CT003 study.

During the ALA-AK-CT002 FUP study 10 SAEs were reported in 8 subjects (3 for subjects treated with BF-200 ALA, 5 for subjects who received MAL). Four SAEs were fatal. The SAEs occurred between about 6 weeks after the last PDT and about 1 year after the last PDT and the investigators considered them unrelated or unlikely related to the PDT. No SAEs were noted during the ALA-AK-CT003 FUP.

New lesions occurred in all patient groups of the pivotal studies, affecting from 41.7% to 56.1% of the patients after 12 months, with the exception of the ALA-AK-CT003 placebo arm, where for unknown reasons the percentage was only 20.6% (Table 6). In the ALA-AK-CT002 study, the percentage of patients developing new AK lesions was higher for non-complete responders than for complete responders (65% vs 36%, 64% vs 43% and 65% vs 31% for BF-200 ALA, MAL, and placebo-treated patients, respectively). Study ALA-AK-CT003 showed similar numbers in the BF-200 ALA group with 39.6% for complete responders vs 47.4% for non-complete responders, but clearly different figures in the placebo group (24.1% vs 0%).

Non-melanoma skin cancers (SCC, BCC) developed in the treatment area only in few patients at a very similar extent in most study groups, with the exception of a slight increase in the ALA-AK-CT002 placebo group (Table 6). No melanomas were reported in both studies. Interestingly, most of the patients with non-melanoma skin cancer were non-complete responders (14/20 in ALA-AK-CT002, 2/4 in ALA-AK-CT003) or had a history of skin diseases including AK for several years (18/20 in ALA-AK-CT002, 4/4 in ALA-AK-CT003).

Discussion

BF-200 ALA is a new nanoscale oil in water emulsion of ALA for PDT which was recently shown to be a very effective and safe treatment option for AK lesions[6;7]. PDT is recommended as a first line therapy for the treatment of AK due to its high efficacy, the possibility to treat extended skin areas and its superior cosmetic outcome compared to other treatment modalities[1]. However, long-term follow-up data of controlled clinical trials are limited and only few publications reported recurrence rates after ALA or MAL-PDT treatment over a longer follow-up period[9;11].

The present publication summarizes 6- and 12-month FUP data collected in two pivotal phase III studies[6;7]. The reported studies compared the clearance and recurrence rates, new lesion formation and cosmetic outcome in AK patients treated with BF-200 ALA or placebo, and one of the studies compared the results for BF-200 ALA with those for a commercially available MAL formulation. The data confirm that PDT is a highly effective and safe therapy

for AK. Both PDT drugs displayed low recurrence rates, in favour of BF-200 ALA over MAL. The probability that complete responders remained cleared 12 months after the last treatment was 0.59 or 0.71 for BF-200 ALA (study ALA-AK-CT002 and ALA-AK-CT003, respectively) and 0.56 for MAL (study ALA-AK-CT002). Although these recurrence rates of BF-200 ALA are not substantially lower than that of MAL, the difference is reflected in all subgroups analyzed, illustrating a general tendency to slightly lower recurrence rates.

Nevertheless, the probability of clearance 12 months after PDT is strongly in favour of BF-200 ALA due to its statistically significantly higher efficacy. These probabilities, denoted p_2*CR_P, were 0.47 for BF-200 ALA versus 0.36 with MAL for all lamps, and 0.53 vs 0.41 for narrow spectrum lamps, respectively, in study ALA-AK-CT002. Thus, calculating a patient's long-term prognosis as the combination of efficacy and recurrence rates demonstrates the strong superiority of BF-200 ALA compared to MAL. It is worth noting that p_2*CR_P values in patients who were completely cleared already after a single PDT, were still better 12 months after BF-200 ALA treatment than 6 months after MAL treatment (Table 5).

The two pivotal trials documented a strong influence of the applied lamp sources on PDT efficacy. Narrow wavelength lamps generated greatly better clinical efficacy than broad wavelength lamps[6;7]. Therefore, it was of particular interest to compare the recurrence rates of these subgroups. For most subgroups, patients illuminated with narrow band LED lamps displayed lower recurrence rates than those illuminated with broad band lamps. Therefore, the advantage of higher efficacy provided by the LED lamps is at least maintained or even enhanced during the 12 months following PDT.

Studies describing recurrence rates of conventional therapies are rare and mostly poorly controlled. The recurrence rates described[13] after one year were similar or worse than those described here. A better data basis is available for PDT drugs, where several authors published FUP results of phase III studies of AK PDT. The life-table analysis, in which the probability p_2*CR_P expresses the likelihood that a patient is completely cleared during treatment and remains cleared of all lesions for 12 months after treatment, should serve as the basis to choose the optimal therapy for the patients. Our data illustrate that 53% (study ALA-AK-CT002) to 68% (study ALA-AK-CT003) of patients treated with BF-200 ALA and LED lamps, and 41% of patients treated with MAL and LED lamps are cleared of all lesions during treatment and remain free of all lesions for at least 12 months after treatment. This treatment success is clearly above the values achieved in controlled trials with Levulan Kerastick (40%)[9], ALA patch (21% to 45%)[11;10], cryotherapy (29%)[11;10] or of a recently approved ingenol mebutate (0.015%) containing gel (20%)[12] (Table 7). In the studies cited here Levulan Kerastick was, according to its product specification, used in combination with blue light, the ALA patch also with LED lamps.

The lesion recurrence rates observed in the 12-month FUP assessments for lesions treated with BF-200 ALA and LEDs are in a similar range (21% in study ALA-AK-CT002) or clearly below (7% in study ALA-AK-CT003) the values provided in the published literature[9;11;14]. On average with all lamps the recurrence rates were 22% in study ALA-AK-CT002 and 17% in study ALA-AK-CT003, respectively. Lesion recurrence rates for MAL were slightly higher with 24% for LED lamps and 25% on average for all lamps. However, it must be taken into consideration that lesion recurrence in study ALA-AK-CT002 is overestimated since, for subjects who received AK therapy between visits or for whom the number of recurrent lesions was not documented, all lesions were classified as recurrent, irrespective of the actual recurrence. This aspect is most relevant in the recurrence evaluation

at FUP visit 2 in which 61% of recurrent lesions in the BF-200 ALA and 74% of recurrent lesions in the MAL group belonged to the aforementioned patient group. All the general tendencies observed for total patient recurrence were paralleled and confirmed by the data obtained when the occurrence of individual lesions was calculated. Here also, recurrence rates with MAL were slightly higher than those for BF-200 ALA in all subgroups.

The assessment of the cosmetic outcome as very good or good for BF-200 ALA and MAL treated patients differed only slightly from the evaluation at the end-of-study visit (BF-200 ALA: 47.6% and 43.1% at the end of study vs 45.0% and 38.9% at FUP visit 2, for ALA-AK-CT003 and ALA-AK-CT002 respectively; MAL: 45.2% vs 41.1%, respectively). Placebo values increased from 25% to 46.9% in study ALA-AK-CT003 and changed from 36.4% to 32.8% in the ALA-AK-CT002 study[6;7]. The lower values in the placebo groups might be influenced by the higher percentage of additional AK therapies applied subsequent to the studies. Application of conventional AK therapies to recurrent patients might also explain the increase of unsatisfactory or impaired values in the verum groups during FUP.

In conclusion, treatment with BF-200 ALA revealed a high efficacy in the treatment of AKs which is maintained over a 1-year follow-up period. Total patient clearance rates are significantly higher with BF-200 ALA than with MAL, and this advantage may even be enhanced by the tendency to lower recurrence rates.

Acknowledgement

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Legend to Fig 1:
Treatment regime of the clinical phases and FUPs of studies ALA-AK-CT002 and ALA-AK-CT003. Assessment of PDT efficacy was scheduled 3 months after PDT. Subsequently, completely cleared patients entered FUP with 2 visits 6 and 12 months after PDT (**A**). In case of residual lesions three months after the first PDT, a second PDT was performed (**B**) with a final assessment of efficacy 3 months later.

Legend to Fig 2:
Allocation of patients in the FUP phases of studies ALA-AK-CT003 (**A**) and ALA-AK-CT002 (**B**). The numbers of patients entering and completing FUP are indicated along with the cause of discontinuation during the FUP.
CR_P: complete responders, i.e. patients without remaining lesions 3 months after the last PDT.

Tables

Table 1 Calculation of life-table estimates for subject-based recurrence rates

Visit name	Visit (i)	$CR_{Pi} = CR_{P(i-1)} - R_i - L_i$	R_i	L_i	$f_i = 1 - R_i/(CR_{Pi} - L_i/2)$	$p_i = p_{(i-1)} * f_i$
3 months after last PDT	0	CR_{P0}	0	0	1	1
Follow-up after 6 months	1	CR_{P1}	R_1	L_1	f_1	p_1
Follow-up after 12 months	2	CR_{P2}	R_2	L_2	f_2	p_2

CR_{P0}:Number of subjects totally cleared of lesions at end-of-study visit 3 months after the last PDT
CR_{Pi}: Number of subjects with complete remission of all AK lesions in the target area(s) at current visit
R_i: Number of subjects with at least one recurrent lesion in target area(s) between preceding and current visit
L_i: Number of subjects lost to follow-up or withdrawn between preceding and current visit
f_i: Probability of remaining cleared for subjects with complete remission at preceding visit
p_i: Probability of remaining cleared up to current visit

Table 2A Overview of Demographics

		No of subjects				
		ALA-AK-CT003		ALA-AK-CT002		
	Population	BF-200 ALA	Placebo	BF-200 ALA	MAL	Placebo
Clinical trial	Patients enrolled in clinical study	122		600		
	Patients randomized	81	41	248	247	76
	FAS/ITT population	80 (100%)	40 (100%)	248 (100%)	246 (100%)	76 (100%)
	Premature discontinuation	4	4	7	7	8
	Complete responders 3 months after last PDT (CR_P, %) after 1st PDT after 2nd PDT	53 (66.3%) 38 (47.5%) 15 (38.5%)	5 (12.5%) 4 (10.0%) 1 (3.0%)	194 (78.2%) 120 (48.4%) 74 (57.8%)	158 (64.2%) 91 (37.0%) 67 (43.2%)	13 (17.1%) 3 (3.9%) 10 (13.7%)
	Totally cleared lesions 3 months after last PDT, n (CR_L, %)	369 (81.1%)	46 (20.9%)	1359 (90.4%)	1295 (83.2%)	182 (37.1%)
FUP	Patients entering FUP (FAS/ITT)	77 (96.3%)	37 (92.5%)	241 (97.2%)	240 (97.6%)	68 (89.5%)
	FUP1	72 (93.5%)	34 (91.9%)	238 (98.8%)	236 (98.3%)	66 (97.1%)
	FUP2	71 (92.2%)	32 (86.5%)	236 (97.9%)	232 (96.7%)	64 (94.1%)
	Patients completing FUP	70 (90.9%)	32 (86.5%)	233 (94.0%)	231 (93.9%)	64 (94.1%)
	Lost to FUP	7	5	8	9	4
	Complete responders entering FUP[a]	53 (66.3%)	5 (12.5%)	192 (77.4%)	157 (63.8%)	13 (17.1%)
	FUP1	51 (63.8%)	4 (10.0%)	188 (75.8%)	154 (62.6%)	13 (17.1%)

	FUP2	49 (61.3%)	4 (10.0%)	185 (74.6%)	154 (62.6%)	13 (17.1%)
	Lesions considered for recurrence rate in FUP, n (%)[b]	353	45	1147	958	84

a: only subjects who were completely cleared 3 months after the last PDT were considered for evaluation of recurrence rates
b: Only lesions of complete responders were considered in all patient groups of study ALA-AK-CT002. If in study ALA-AK-CT002 patients were treated for AK between FUP visits or the number of recurrent lesions was not noted, all lesions of the patient were counted as recurrent.

Table 2B: Summary of patient characteristics entering FUP (ITT/FAS)

	ALA-AK-CT003		**ALA-AK-CT002**		
Study arm	BF-200 ALA (N=77)	Placebo (N=37)	BF-200 ALA (N=241)	MAL (N=240)	Placebo (N=68)
Sex, N (%)					
Male N (%)	69 (89.6%)	29 (78.4%)	208 (86.3%)	199 (82.9%)	54 (79.4%)
Female N (%)	8 (10.4%)	8 (21.6%)	33 (13.7%)	41 (17.1%)	14 (20.6%)
Age (years)					
Mean ± SD	70.4 ± 5.2	71.3 ± 6.4	70.1 ± 7.2	71.0 ± 7.0	71.7 ± 6.8
Range	58-82	60-85	39-87	44-85	51-84
Severity of AK at baseline[a], N					
Mild (Grade I)	15	2	33	37	3
Moderate (Grade II)	38	3	159	120[b]	10
Target area, N					
A (face and forehead)	31	2	120	107	4
B (bald scalp)	13	3	47	23	5
A+B	9	0	25	27	4
Light spectrum , N					
Narrow	27	2	104	84	5
Broad	26	3	88	73	8

a: patients with at least one AK assessed with Grade II at start of clinical trial;
b: one severe (Grade III) lesion included

Table 3: Patient-based life table

A: Number of subjects still cleared at 6- and 12-month follow-up visits in study ALA-AK-CT003

	BF-200 ALA (N=53)			Placebo (N=5)		
	Subjects completely cleared[a]	**p_i**	**p_i*CR_P**	**Subjects completely cleared**[a]	**p_i**	**p_i*CR_P**
FUP1	82.4%	0.827	0.548	50.0%	0.556	0.069
FUP2	69.4%	0.706	0.468	50.0%	0.556	0.069

p_i: Probability that a completely cleared patient remains completely cleared up to FUP1 or FUP2;
pi* CR_P: Probability that a patient is fully cleared from all lesions during PDT and remains totally cleared until the follow-up visit (product of pi and efficacy rate at the end of the clinical trial)
a: The percentage is calculated according to the number of patients at the respective visit.

B: Number of subjects still cleared at 6- and 12-month follow-up visits in study ALA-AK-CT002

	BF-200 ALA (N=192)			MAL (N=157)			Placebo (N=13)		
	Subjects completely cleared[a]	**p_i**	**p_i*CR_P**	**Subjects completely cleared**[a]	**p_i**	**p_i*CR_P**	**Subjects completely cleared**[a]	**p_i**	**p_i*CR_P**
FUP1	80.9%	0.812	0.647	81.8%	0.821	0.537	84.6%	0.846	0.162
FUP2	58.4%	0.592	0.472	55.2%	0.555	0.363	76.9%	0.769	0.147

p_i: Probability that a completely cleared patient remains completely cleared up to FUP1 or FUP2;
pi* CR_P: Probability that a patient is fully cleared from all lesions during PDT and remains totally cleared until the follow-up visit (product of pi and efficacy rate at the end of the clinical trial)
a: The percentage is calculated according to the number of patients at the respective visit.

Table 4: Recurrent lesions at 6 and 12 months FUP

		BF-200 ALA (ALA-AK-CT003)			BF-200 ALA (ALA-AK-CT002)[a]			MAL (ALA-AK-CT002)[a]		
	Subgroup	**Recurrent[b]**	**p_i**	**p_i*CR$_L$**	**Recurrent[b]**	**p_i**	**p_i*CR$_L$**	**Recurrent[b]**	**p_i**	**p_i*CR$_L$**
Overall										
FUP 1	N/A	7.4%	0.928	0.752	7.0%	0.931	0.733	6.6%	0.935	0.589
FUP 2[c]	N/A	16.7%	0.843	0.684	21.7%	0.855	0.525	25.4%	0.813	0.401
Light spectrum										
FUP 1	Narrow	1.8%	0.982	0.945	4.1%	0.960	0.818	5.2%	0.949	0.622
	Broad	12.7%	0.878	0.620	11.2%	0.890	0.633	8.4%	0.916	0.554
FUP 2[c]	Narrow	7.0%	0.932	0.897	20.6%	0.839	0.591	24.1%	0.813	0.435
	Broad	26.4%	0.760	0.536	23.0%	0.883	0.445	27.2%	0.812	0.363

p_i: Probability that a completely cleared lesion remains completely cleared up to FUP1 or FUP2;
p_i*CR_L: Probability that a lesion is fully cleared during PDT and remains totally cleared until the follow-up visit (product of pi and efficacy rate at the end of the clinical trial);
a: Only lesions of complete responders are considered;
b: The percentage is calculated according to the number of lesions at the respective visit;
c: Recurrences are cumulated;
N/A: not appropriate;

Table 5: Patient subgroups completely cleared at 6 and 12 months FUP

Subgroup		Visit	BF-200 ALA (ALA-AK-CT003)			BF-200 ALA (ALA-AK-CT002)			MAL (ALA-AK-CT002)		
			Patients still completely cleared[a]	p_i	p_i*CR_P	Patients still completely cleared[a]	p_i	p_i*CR_P	Patients still completely cleared[a]	p_i	p_i*CR_P
Light spectrum	Broad	FUP1	75.0%	0.760	0.403	74.7%	0.750	0.545	76.7%	0.767	0.483
		FUP2	60.9%	0.630	0.334	56.3%	0.567	0.412	50.7%	0.507	0.319
	Narrow	FUP1	88.9%	0.889	0.774	86.1%	0.864	0.749	86.4%	0.867	0.592
		FUP2	76.9%	0.775	0.675	60.2%	0.613	0.531	59.3%	0.597	0.408
AK severity at baseline	Grade I	FUP1	100%	1.000	0.789	78.1%	0.788	0.667	86.5%	0.865	0.821
		FUP2	80.0%	0.800	0.632	69.7%	0.697	0.590	64.9%	0.649	0.615
	Grade II	FUP1	75.0%	0.757	0.471	81.4%	0.816	0.643	80.3%	0.807	0.482
		FUP2	64.7%	0.669	0.417	55.9%	0.569	0.448	52.1%	0.525	0.313
Target area	A: face /forehead	FUP1	79.3%	0.800	0.564	82.9%	0.832	0.693	83.7%	0.840	0.651
		FUP2	71.4%	0.729	0.514	59.6%	0.607	0.506	60.6%	0.609	0.472
	B: bald scalp	FUP1	92.3%	0.923	0.545	76.6%	0.766	0.554	82.6%	0.826	0.352
		FUP2	84.6%	0.846	0.500	57.4%	0.574	0.415	52.2%	0.522	0.222
	A + B	FUP1	77.8%	0.778	0.500	79.2%	0.800	0.625	74.1%	0.741	0.417
		FUP2	37.5%	0.419	0.269	54.2%	0.554	0.433	37.0%	0.370	0.208
Complete responder	After 1 PDT	FUP1	89.2%	0.893	0.424	86.4%	0.864	0.423	83.1%	0.832	0.312
		FUP2	71.4%	0.726	0.345	65.5%	0.659	0.323	59.6%	0.596	0.224

p_i: Probability that a completely cleared patient remains completely cleared up to FUP1 or FUP2;
pi^* CR_P: Probability that a patient is fully cleared from all lesions during PDT and remains totally cleared until the follow-up visit (product of pi and efficacy rate at the end of the clinical trial)
a: The percentage is calculated according to the number of patients at the respective visit.

Table 6: New lesions and skin cancer in the target areas

	ALA-AK-CT003		ALA-AK-CT002		
	BF-200 ALA	Placebo	BF-200 ALA	MAL	Placebo
New AK					
FUP 1 (6 months)	16/72 (22.2%)	4 /34 (11.8%)	51/237 (21.5%)	56/236 (23.7%)	18/66 (27.3%)
FUP 2[a] (12 months)	14/71 (19.7%)	3/32 (9.4%)	48/234 (20.5%)	59/231 (25.5%)	19/64 (29.7%)
Overall	30/72 (41.7%)	7/34 (20.6%)	99/237 (41.8%)	115 (48.7%)	37/66 (56.1%)
Non-melanoma skin cancer					
FUP 1 (6 months)	2/72 (2.8%)	1/34 (2.9%)	3/237 (1.3%)	2/236 (0.8%)	3/66 (4.5%)
FUP 2[a] (12 months)	1/71 (1.4%)	0	5/234 (2.1%)	6/231 (2.6%)	1/64 (1.6%)
Overall	3/72 (4.2%)	1/34 (2.9%)	8/237 (3.4%)	8/236 (3.5%)	4/66 (6.3%)

Numbers indicate the affected patients/ all patients assessed at the particular FUP visit.
a: Data for FUP visit 2 reflect the number of patients who developed new lesions or non-melanoma skin cancer since FUP visit 1.

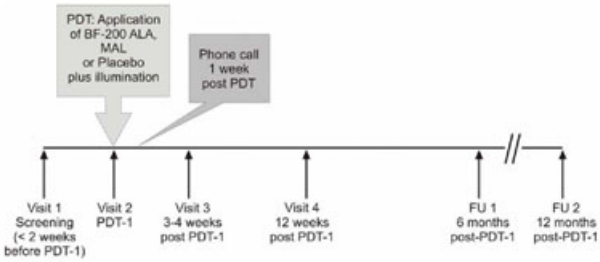
Table 7: Results of long-term Follow-ups studies using LED lamps

	ALA[a] 6;7 **(BF-200 gel, 78 mg/g)**	**MAL**[a] 7 **(cream, 160 mg/g)**	**ALA**[a] 10;11 **(patch, 2 mg/cm²)**	**ALA**[b] 9 **(2-compound system, 156 mg/g)**	**Cryo** 10;11	**Ingenol mebutate** 12 **(gel, 150 µg/g)**
% of completely cleared patients at the end of clinical study						
Completely cleared patients	CT002: 85%[c] CT003: 96%[d]	CT002: 68%[c]	AK3: 62%[c] AK4: 67%[d]	60%[d,e]	52%[c]	42%[g]
Estimated patient-wise AK clearance rate related to number of patients pre-treatment 12 months after last treatment						
Completely cleared patients	CT002: 53%[a] CT003: 68%[a]	CT002: 41%[a]	AK3: 21%[a] AK4: 45%[a]	40%[f]	29%	20%[h]

a: treated with LED lamps; b: using BlueU (417 nm) lamp;
c: FAS/ITT; d:PP population; e: 3-5 months after last treatment; f: 10-12 months after last treatment; g: 57 days after last application ; h: 57 days + 12 months; concentrations referred to free acid.

Figure 1 Treatment regime in clinical part and FUP of studies ALA-AK-CT002 and ALA-AK-CT003

A Treatment regime for patients with complete response after one PDT (study ALA-AK-CT003 without MAL)



B Treatment regime for patients with complete response after two PDTs (study ALA-AK-CT003 without MAL)

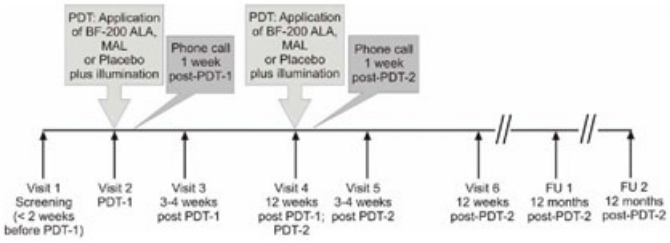


Figure 2A

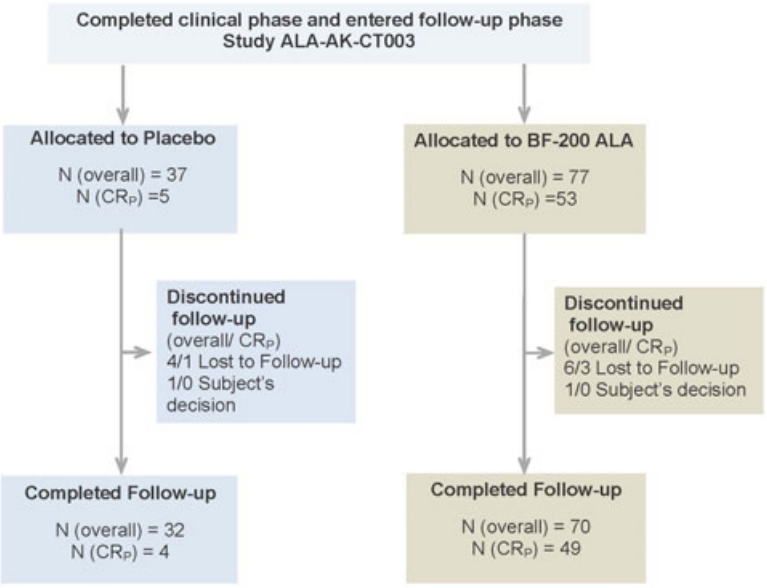
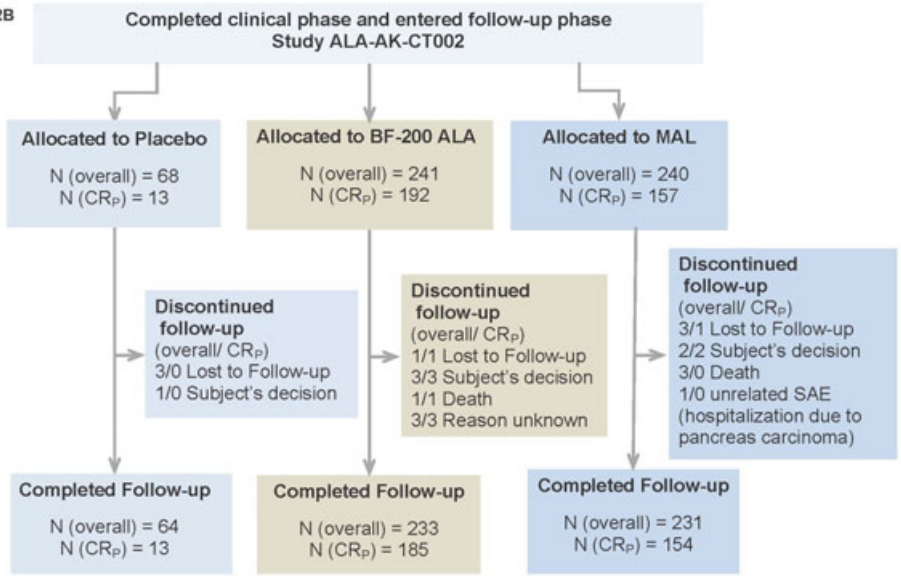


Figure 2B


Completed clinical phase and entered follow-up phase
Study ALA-AK-CT002
Allocated to Placebo
N (overall) = 68
N (CRP) = 13
Allocated to BF-200 ALA
N (overall) = 241
N (CRP) = 192
Allocated to MAL
N (overall) = 240
N (CRP) = 157
Discontinued follow-up
(overall/ CRP)
3/0 Lost to Follow-up
1/0 Subject's decision
Discontinued follow-up
(overall/ CRP)
1/1 Lost to Follow-up
3/3 Subject's decision
1/1 Death
3/3 Reason unknown
Discontinued follow-up
(overall/ CRP)
3/1 Lost to Follow-up
2/2 Subject's decision
3/0 Death
1/0 unrelated SAE
(hospitalization due to pancreas carcinoma)
Completed Follow-up
N (overall) = 64
N (CRP) = 13
Completed Follow-up
N (overall) = 233
N (CRP) = 185
Completed Follow-up
N (overall) = 231
N (CRP) = 154