15 December 2016
EMA/749508/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ameluz

International non-proprietary name: 5-aminolevulinic acid

Procedure No. EMEA/H/C/002204/II/0024

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

∞	infinity
5-FU	5-fluorouracil
AK	actinic keratosis
ALA	amino-levulinic acid
BCC	basal cell carcinoma
BMI	body mass index
χ^2	chi square
C	Caucasian
C	carbon
CI	confidence interval
CR	clearance rate
CSR	clinical study report
Eg	*exempli gratia*, for example
F	women
FAS	full-analysis set
FASFU	Full analysis set follow up
HPLC-FD	high-liquid performance chromatography with fluorescence detection
HPLC-MS/MS	high-liquid performance chromatography with tandem mass spectrometry
ie	*id est*, that is
ITT	intent-to-treat
LED	light emitting diode
LLOQ	lower limit of quantification
M	men
MAL	methyl-amino-levulinate
MedDRA	Medical Dictionary for Regulatory Activities
N	number
N/A	not applicable
NMSC	non-melanoma skin cancer
NR	not reported
$^1O_2$	singlet oxygen
OECD	Organisation for Economic Co-operation and Development
P	probability
PDT	photodynamic therapy
PK	pharmacokinetic
PP	per-protocol
PPS	per-protocol set
PPSFU	Per protocol safety follow up
PpIX	protoporphyrin IX
R	randomized
ROS	reactive oxygen species
SAF	Safety Analysis Set
SCC	squamous cell carcinoma
SD	standard deviation
vITT	valid for intent-to-treat analysis
vs	*versus*, as opposed to

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Biofrontera Bioscience GmbH submitted to the European Medicines Agency on 27 July 2016 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication from "Treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2; see section 5.1) and of field cancerization" to the following:
"Treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2; see section 5.1) and of field cancerization in adults.
Treatment of non-aggressive basal cell carcinoma (primary superficial or nodular basal cell carcinoma or mixed types of both, with good or intermediate prognosis) on the face, scalp, neck, trunk and extremities in adults including the elderly."

Consequently, sections 4.1, 4.2, 4.4, 4.6, 4.8 and 5.1 of the SmPC are updated. Editorial changes have been proposed in sections 2, 4.5, 4.7, 5.2, 6.5 and 9 of the SmPC. The Package Leaflet and Labelling are updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and PRAC Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Harald Enzmann PRAC-Rapporteur: Martin Huber

Timetable	Actual dates
Submission date	27 July 2016
Start of procedure	13 August 2016
CHMP Rapporteur Assessment Report	7 October 2016
PRAC Rapporteur Assessment Report	11 October 2016
PRAC members comments	19 October 2016
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	27 October 2016
CHMP members comments	25 October 2016
Updated CHMP Rapporteur's Assessment Report	4 November 2016
Request for supplementary information and extension of timetable adopted by the CHMP on	10 November 2016
MAH's responses submitted to the CHMP on	22 November 2016
Joint Rapporteur – PRAC Rapporteur's assessment report on the MAH's responses circulated on	30 November 2016
CHMP and PRAC member comments	05 December 2016
Joint Rapporteur – PRAC Rapporteur's updated assessment report on the MAH's responses circulated on	08 December 2016
CHMP opinion	15 December 2016

2. Scientific discussion

2.1. Introduction

BCC represents the most common non-melanoma skin cancer worldwide affecting mainly adult (age ≥40), fair-skinned individuals[1,2]. BCCs develop predominately in sun-damaged skin and occur with an incidence rate of 1,406/100,000 in the United States (US) (1998/99), 3,252/100,000 in Queensland/Australia (1997) and 143/100,000 in Germany (2004). Incidence rates are dramatically increasing, e.g. in Denmark from 34 to 91 /100,000 cases in males and from 27 to 97 /100,000 cases in females between 1978 and 2007, and in the Netherlands incidences increased from 40 to 148/100,000 in males and from 34 to 141/100,000 in females between 1978 and 2008[3].

BCCs are locally invasive tumours, and metastases occur in less than 1 in 10,000 tumours[2]. Though 70% of primary BCC cases occur on the skin of the head or neck, 85% of metastatic cases and 90% of recurrent cases occur at these sites. Composed of proliferating keratinocytes from basal cells of the epidermis, BCC generally demonstrates a relatively innocuous course, with slow growth and only minimal local extension. Accordingly, this disease typically has a favourable prognosis. The WHO distinguishes non-aggressive BCCs and aggressive forms according to their fundamentally different biological characteristics as well as their size and body localization[1,2,4]. In these 2 groups, the WHO includes superficial, nodular (solid), micronodular, infiltrating, and fibroepithelial BCCs, BCC with adnexal differentiation, and basosquamous and keratotic BCCs[2]. Primary nodular and superficial BCC (sBCC) or mixed sBCC and nodular BCCs (nBCCs) are the prototypical varieties of BCC and tend to be less aggressive in general (good to intermediate prognosis)[1,5]. Approximately 10-30% of BBCs are diagnosed as sBCCs, erythematous patches with pearly border with a superficial erosion appearing mainly in the trunk area, while nBCCs make up 60-80% of the BCCs and occur most frequently on the head as elevated nodules associated with telangiectasia which can become ulcerative or cystic. Both types of BCCs have district histopathological features. sBCC consist of superficial lobules of basaloid cells confined to the papillary epidermis which project from the epidermis or from the sides of follicles or eccrine ducts into the dermis and surrounded by stroma. nBCC appear as large basaloid lobules that project deeper than the reticular dermis[2]. Risk factors which influence the prognosis of BCC include tumour size and site, definition of the margins, histological subtype, features of aggression (perivascular perineural involvement), failure to other treatment and immunosuppression[4]. The fibroepithelioma of Pinkus consists of usually only one bit occasionally of several raised, moderately firm, slightly pedunculated nodules, covered by smooth, slightly reddened skin. Clinically, they resemble fibromas. The most common location is the neck[6]. The histopathology is characterized by an arborising network of cords of basaloid cells that extend downwards from the epidermis and create a fenestrating pattern. There are strands of basaloid cells that surround fibrovascular stroma. Ductules may be present in some of the cords, which may represent extension of the tumor down pre-existing eccrine ducts. The cords also are associated with small follicle-like bulbs that project into the surrounding connective tissue[2].

[1] Walling, H.W., Fosko, S.W., Geraminejad, P.A., Whitaker, D.C. & Arpey, C.J. (2004) Aggressive basal cell carcinoma: presentation, pathogenesis, and management. Cancer Metastasis Rev, 23, 389-402.
[2] LeBoit, P.B., G.; Weedon, D.; Sarasin, A. (2006) Pathology and Genetics of Skin Tumours. World Health Organization Classification of Tumours.
[3] Trakatelli, M., Morton, C., Nagore, E., Ulrich, C., Del Marmol, V., Peris, K. & Basset- Seguin, N. (2014) Update of the European guidelines for basal cell carcinoma management. Eur J Dermatol, 24, 312-329.
[4] Telfer, N.R., Colver, G.B. & Morton, C.A. (2008) Guidelines for the management of basal cell carcinoma. Br J Dermatol, 159, 35-48.
[5] Managemnent of basal cell carcinoma (BCC) in adults: ANAES – French National Agency for Accreditation and Evaluation in Healthcare (Guidelines Department); 2004.
[6] Kirkham N. Tumors and cysts of the epidermis. In: Elder D, editor. Lever's histopathology of the skin. 2. 9 ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 836-49.

Table 1: Classification of BCC subtypes according to prognosis[5]

Poor prognosis	Good prognosis	Intermediate prognosis
• Clinical forms: morpheiform or ill-defined • Histological forms: aggressive • Recurrent forms (apart from superficial BCC) • nBCC >1cm in high risk zone	• Superficial primary BCC • Pinkus tumor • Nodular primary nBCC: ○ <1 cm in intermediate risk area ○ <2 cm in low risk area	• Superficial recurrent BCC • nBCC ○ <1 cm in high risk area ○ >1 cm in intermediate risk area ○ >2 cm in low risk area

BCC: basil cell carcinoma; nBCC: Nodular basal cell carcinoma.
Low risk area: trunk and limbs; intermediate risk area: forehead; cheek, chin, scalp and neck; high risk area: nose and periorificial areas on the head and neck. (Source: [5] [11])

The probability of recurrence after treatment is used to categorise BCC lesion into either low risk or high risk of progression. Following treatment, less than a third of recurrences present the first year after follow up, 50% within 2 years and 66% within 3 years. The cumulative risk is between 33-70% and patients who are disease free after 3 years have a low risk of further developing BCC[4].

According to the National Comprehensive Cancer Network guidelines on treatments for BCC, the main objective is achieving maximal preservation of function and cosmetics. European guidelines for the management of BCC list a variety of treatment options aiming at eradicating the tumour while ensuring an acceptable cosmetic outcome for the patients[4, 7, 3, 8] . Among therapies recommended for low risk early BCCs, these include surgical excision, radiotherapy (low wave X-ray, brachytherapy, high energy radiotherapy) and 5-fluorouracil, photodynamic therapy (PDT), particularly for the treatment of large or multiple lesions. In several European countries, methyl aminolevulinate (MAL, Metvix) with PDT has been approved for the treatment of superficial and/or nodular basal cell carcinoma unsuitable for other available therapies due to possible treatment related morbidity and poor cosmetic outcome; such as lesions on the mid-face or ears, lesions on severely sun damaged skin, large lesions, or recurrent lesions.

5-Aminolevulenic acid (BF-200 ALA, Ameluz) was developed as a nanoemulsion-based gel formulation, initially for the treatment of actinic keratosis (AK) with PDTc. In the European Union (EU), a Community Marketing Authorization was granted for Ameluz in December 2011 for the treatment of mild to moderate AKs in the face and scalp (EU/1/11/740/001).

The MAH applied for the following indication:

- Treatment of non-aggressive basal cell carcinoma (primary superficial or nodular basal cell carcinoma or mixed types of both, with good or intermediate prognosis) on the face, scalp, neck, trunk and extremities in adults including the elderly.

The final agreed indication is as follows:

- Treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults.

Posology in adults

For treatment of basal cell carcinoma (BCC), two sessions of photodynamic therapy shall be administered for one or multiple lesions with an interval of about one week between sessions. Basal cell carcinoma lesions shall be evaluated three months after last treatment. Treated lesions that have not completely resolved after 3 months shall be retreated.

[7] Morton, C.A., Szeimies, R.M., Sidoroff, A. & Braathen, L.R. (2012a) European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications - actinic keratoses, Bowen's disease, basal cell carcinoma. J Eur Acad Dermatol Venereol.
[8] Morton, C.A., Szeimies, R.M., Sidoroff, A. & Braathen, L.R. (2015) Response to Letter to the editor: 'European guidelines for topical PDT part 1. JEADV 2013;27:536-544' DOI: 10.1111/jdv.12258. J Eur Acad Dermatol Venereol, 29, 1451-1452.

Method of administration

Nodular BCC lesions are often covered by an intact epidermal keratin layer which should be removed. Exposed tumour material should be removed gently without any attempt to excise beyond the tumour margins.

The illumination dose remains the same as for actinic keratosis (AK).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

No ERA was submitted. The applicant submitted a justification for the absence of an ERA.

2.2.2. Discussion on non-clinical aspects

The lack of non-clinical data is acceptable as the non-clinical aspects have been evaluated previously for the initial marketing authorisation. Since the active substance 5-aminolevulinic acid is an amino acid and an intermediate in basic biochemical pathways, it is accepted that an environmental risk assessment is deemed not necessary. This approach is supported by the guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00 corr 2) where it is stated that amino acids are exempted from the requirement for a detailed environmental risk assessment as they are unlikely to result in significant risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

The lack of non-clinical data is acceptable as the non-clinical aspects with the product have been assessed previously. No further studies are considered necessary.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID EudraCT no ClinicalTrials.gov Identifier	Study type	Sponsor	Condition	Title	Status
013-003241-42 NCT02144077 (ALA-BCC-CT008) follow-up	Phase III	Biofrontera Bioscience GmbH, Germany	BCC	A randomized, observer blind, multinational Phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz) in comparison to Metvix in the treatment of non-aggressive basal cell carcinoma (BCC) with photodynamic therapy (PDT)	Start Date: 2013-12-23 Follow-up ongoing until 2020

2.4. Clinical efficacy

2.4.1. Main study

ALA-BCC-CT008: A randomized, observer blind, multinational phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz) in comparison to Metvix in the treatment of non-aggressive basal cell carcinoma (BCC) with photodynamic therapy (PDT)

Methods

Study participants

Main inclusion criteria

- Men or women ≥18 years of age (inclusive).
- Willing and able to sign the Informed Consent Form. A study-specific informed consent was obtained in writing for all patients before starting any study procedures.
- Presence of 1 to 3 primary BCC lesions in the face/forehead, bald scalp, extremities and/or neck/trunk, all of which were, according to the clinical judgment of the investigator, likely to fulfill the criteria for positive outcome of the histological assessment (non-aggressive BCCs comprising primary superficial, nodular, or mixed superficial/nodular BCC (sBCC/nBCC) with a thickness ≤2 mm) of BCC by biopsy taken at screening were allowed to be included in the study. Lesions assessed as non-eligible by biopsy taken at screening were to be excised by surgery or removed by cryotherapy in a timely manner. Other treatments were not allowed for these lesions.
- The diameter of each eligible lesion was to range between ≥ 0.5 cm and ≤2 cm; the total maximal treated area was not be larger than approximately 10 cm^2 (including a 0.5 - 1.0 cm margin surrounding each lesion).
- Target BCC lesions were to be discrete and quantifiable: the diameter of each BCC lesion must be not smaller than 0.5 cm and not larger than 2.0 cm. To describe irregular lesions (ellipsoidal), investigators will measure the major and minor axes. Both axes must be between the minimum of 0.5 cm and the maximum of 2.0 cm. The thickness of the BCC according to the histological examination must not be more than 2 mm. The lesions must be located within 1-2 treatment areas. Target lesions were to be placed within maximal 2 illumination areas (the illumination area was defined by the effective illumination area of the BF-RhodoLED (light emitting diode) device with approximately 6 x 16 cm).
- Patients displaying non-eligible lesions by biopsy taken at screening were to be included in the study if at least one lesion was eligible and the non-eligible lesions were at least 10 cm apart from the eligible lesion(s). In such patients, the non-eligible lesions were to be timely removed by surgery or cryotherapy

- Willingness to undergo biopsy at the end of the observer blind part of the study 12 weeks after the last PDT in case of partial or non-responding lesions.
- Willingness to receive up to 4 PDTs within 3.5 months.
- Women of childbearing potential were permitted to participate only if they had a negative serum pregnancy test at screening and a willingness to use a highly effective method of contraception during the observer blind part of the study.

Main exclusion criteria

- History of hypersensitivity to 5-ALA or any ingredient of BF-200 ALA, MAL or any ingredient of Metvix cream, including arachis oil, or to peanut or soya.
- Hypersensitivity to porphyrins.
- Current treatment with immunosuppression therapy.
- Presence of porphyria.
- Presence of BCC lesions on embryonic fusion planes (H-zone).
- Presence of more than 3 BCCs.
- Presence of malignant or benign tumors of the skin other than nonaggressive BCC within the treatment area (e.g. malignant melanoma, squamous cell carcinoma [SCC], aggressive BCC clearly diagnosed at screening visit by clinical assessment) within the last 12 weeks.
- Gorlin Syndrome or Xeroderma pigmentosum.
- Presence of photodermatoses.
- Treatment of lesions (actinic keratosis [AK], BCC, SCC, Bowens disease, melanoma) ≤12 weeks prior to first PDT, except physical treatments (e.g. cryosurgery, excision surgery) that were not allowed ≤6 weeks prior to first PDT (Visit 2).
- Presence of inherited or acquired coagulation defect.
- Start of intake of medication with hypericin or systemically-acting drugs with phototoxic or photoallergic potential within 8 weeks prior to screening.
- Clinically relevant cardiovascular, hepatic, renal, neurologic, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult.
- Evidence of clinically significant (CS), unstable medical conditions, such as:
    - Metastatic tumor or tumor with high probability of metastatic spread
    - Cardiovascular disease (New York Heart Association [NYHA] class III, IV)
    - Immunosuppressive condition
    - Hematologic, hepatic, renal, neurologic, or endocrine condition
    - Collagen-vascular condition
    - Gastrointestinal condition
- Topical treatment with 5-ALA or MAL outside the treatment area during the observer blind part of the study.

- Any topical treatment including diclofenac and immunomodulatory agents (e.g. imiquimod, ingenol mebutate) 12 weeks prior to the first PDT session and during the observer blind part of the study.
- Any physical treatment during the observer blind part of the study within the treated target area(s) with the exception of lesion(s) that could not be confirmed to be eligible by biopsy at screening and that were located at a distance of ≥10 cm to a suitable lesion. These lesions were to be excised surgically or removed by cryotherapy in a timely manner and were not allowed to be treated by PDT in the observer blind part of the study.

Treatments

For each patient, the study consisted of 2 PDT treatments (PDT-1 and PDT-2) approximately 1 week apart. Patients were evaluated 12 weeks after PDT-2 and according to response, the duration of study treatment plus observation was as follows:

- Complete responders (lesions totally cleared clinically): no further treatment for a total treatment and observation duration of 13 weeks.
- Partial or non-responders: 2 additional PDTs in a second PDT cycle for a total treatment and observation duration of 26 weeks

Definition of the treatment region

Non-aggressive BCC located in 1 or 2 separate illumination areas will be treated with PDT in this study. The target areas are defined as the whole face (but without H-zone including eg eyes, ears, temporal area, nose, and mouth, see Appendix B) and the forehead (Target area A), the bald scalp (Target area B), neck/trunk (Target area C) and extremities (Target area D). Only non-aggressive BCC lesions located in these target areas will be treated and analysed.

The overall treatment area (from up to 2 areas out of the Target areas A to D) should contain at least 1 but not more than 3 distinct eligible BCC lesions of together maximal approximately 10 cm2 (including 0.5 – 1.0 cm of surrounding tissue).

Clinical criteria for diagnosis of non-aggressive BCC

Patients must have at least 1 but not more than 3 clinically typical, visible, non-aggressive BCC lesions, each with a maximal thickness of 2 mm, within 1 to 2 treatment areas of together maximally approximately 10 cm2 to be eligible for participation in the study in the respective target areas.

Objectives

Primary objective:
To compare the efficacy of BF-200 ALA (also referred to as Ameluz) containing 7.8% 5 aminolevulinic acid (5-ALA) as active ingredient), with the marketed product Metvix, containing 16% methyl-aminolevulinate (MAL) as active ingredient in the treatment of thin (≤2 mm thickness), non-aggressive basal cell carcinoma (BCC) with photodynamic therapy (PDT).

Secondary objectives:
To evaluate the safety and secondary efficacy parameters related to BF-200 ALA or Metvix for treatment of thin, non-aggressive BCC with PDT and to evaluate the relationship between lesion complete response and lesion thickness at baseline.

Outcomes / endpoints

Efficacy

Primary efficacy variable:

The primary efficacy variable is the overall patient complete response rate assessed 12 weeks after the last PDT.

- An overall complete responder is defined as a patient in whom all treated lesions are cleared after the last PDT.
- The clearance rate of BCC lesions per patient (determined by clinical evaluation) in the treatment area will be measured by comparing the BCC lesion count at baseline with the count at Visit 4, Visit 5, Visit 7, and Visit 8 and during FU visits. A BCC lesion is considered "cleared" if it disappears completely, as assessed visually, ie there are no typical clinical signs of BCC visible.

Secondary efficacy variables:

- Lesion complete response (completely cleared individual lesions) assessed 12 weeks after the last PDT.
- Reduction of total lesion area (summation of sizes of all treated lesions) per patient, assessed 12 weeks after the last PDT.
- Patient complete response (complete clearance of all treated lesions) assessed 12 weeks after PDT-2.
- Overall cosmetic outcome 12 weeks after the last PDT.

Tertiary efficacy variables:

- Lesion complete response (completely cleared individual lesions) assessed 12 weeks after PDT-2.
- Reduction of total lesion area (summation of sizes of all treated lesions) per patient, assessed 12 weeks after PDT-2.
- The change in skin quality assessments compared to baseline assessed 12 weeks after the last PDT.
- Patient's satisfaction 12 weeks of the overall cosmetic outcome after last PDT was to be assessed at the end of the observer blind part of the study (12 weeks after PDT-2 [Visit 5] or 12 weeks after PDT-4 (visit 8) if re-treated [Visit 8]), and at the FU visits using a 5-point scale as follows:
    - 0 = very good
    - 1 = good
    - 2 = satisfactory
    - 3 = unsatisfactory
    - 4 = impaired
    - In addition, patients were to be asked at these visits if they would choose this treatment in the future (e.g. in case of recurrence).

Safety:

- Exposure: Number of PDT sessions
- PDT details (e.g. incubation time of IMP, duration of illumination and percentage of maximal light intensity, distance between illumination source and treatment area, interruptions/pauses, interferences/relief measures)
- Frequency and extent of treatment-emergent adverse events (TEAEs), including serious TEAEs (i.e. adverse events [AEs] or serious AEs [SAEs] with onset or worsening after first treatment with

randomized IMPs) that occurred during the observer blind part of the study. At the FU visits (to be reported separately), any local AEs or conditions that may be relevant for proper assessment of the recurrence rate of the treated BCC lesions were to be documented, and SAEs that occurred up to 12 months after the last PDT were also to be documented.

- Frequency and extent of TEAEs rated by the investigator as skin reactions or by the patient as local discomfort or pain in the treatment area and assessed by the investigator/patient for severity during and after PDT.
- Safety laboratory
- Vital signs
- Physical examinations
- Local discomfort and pain reported and assessed by patients (patient questionnaire in the electronic case report form [eCRF]) during/immediately after PDT, and the investigator's assessment of local skin reactions

Sample size

Originally, it was planned to randomize 360 patients with 180 patients in each treatment group. However, during the blinded monitoring of the study, a higher overall response was observed requiring fewer patients to demonstrate non-inferiority. The sponsor therefore requested a re-assessment be performed and a sample size re-estimated leading to a total of 272 patients planned to be randomized: 136 patients in each group.

Randomisation

The study was randomised in a 1:1 ratio to either the 5-aminolevulenic acid group or ethyl-aminolevulinate group.

Blinding (masking)

This study was performed in an observer blind manner. The study could not be performed in a double blind manner because BF-200 ALA has a different consistency than the comparator Metvix. To guarantee the blind status of the investigator assessing efficacy and safety at all visits after each PDT cycle, a second investigator or delegated person performed the PDT treatment and all safety evaluations at the visits when PDT was performed (including the illumination period).

Statistical methods

The study was divided in 2 parts: an observer blind part consisting of a screening period (up to 2 weeks) and a treatment/observation period (up to 6.5 months), and a follow-up (FU) part (up to 57 months) for a total study duration for each patient of approximately 61 to 64 months, depending on patient response to treatment. Complete responders (lesions totally cleared clinically) 12 weeks after PDT-2 entered the FU part of the study for a total duration of approximately 61 months. Partial or non-responders 12 weeks after PDT-2 were retreated with the same medication by applying 2 additional PDTs in a second PDT cycle and then entered FU (as full responders or as partial or non-responders getting additional treatment according to the choice of the investigator) for a total duration of approximately 64 months. The end of this study was expected to be approximately in the second half of 2020.

Analysis sets

- Enrolled set: All patients enrolled in this study.

- Randomized set (RAND): All patients randomized to IMP irrespective of whether they received IMP or not. The RAND is the analysis set for the summary of patient discontinuation.
- Safety analysis set (SAF): All patients treated at least once with IMP. The assignment of patients to the treatment groups will be as actually treated. The SAF is the analysis set for all safety analysis.
- Full analysis set (FAS): all patients randomized and treated at least once with the IMP after randomization. In accordance with the intent-to-treat principle, the assignment of patients to the treatment groups was randomized.
- Per-protocol (PP) analysis set: All patients of the FAS without any major protocol deviations. The PP set is the primary analysis set for the primary efficacy endpoint

The primary efficacy analysis is defined as the comparison of BF-200 ALA and Metvix with regard to the overall patient complete response assessed 12 weeks after the last PDT.

The primary null hypothesis (H01, one-sided) is that the overall patient complete responder rate assessed 12 weeks after the last PDT for patients treated with BF-200 ALA is lower than the corresponding responder rate for patients treated with Metvix minus the non-inferiority margin of $\Delta = 15\%$:

H01: $rALA < rMetvix - \Delta$

where rALA denotes the rate of responders in the BF-200 ALA group, rMetvix denotes the rate of responders in the Metvix group, and $\Delta = 15\%$ the absolute non-inferiority margin.

The primary alternative hypothesis (H11 , one-sided) is that the overall patient complete responder rate assessed 12 weeks after the last PDT for patients treated with BF-200 ALA is not worse than the corresponding responder rate for patients treated with Metvix by more than the non-inferiority margin Δ:

H11: $rALA \geq rMetvix - \Delta$

The method of Farrington and Manning for testing non-inferiority of differences of proportions[9] will be used to test the primary hypothesis on a significance level of 2.5% (0.025, one sided).

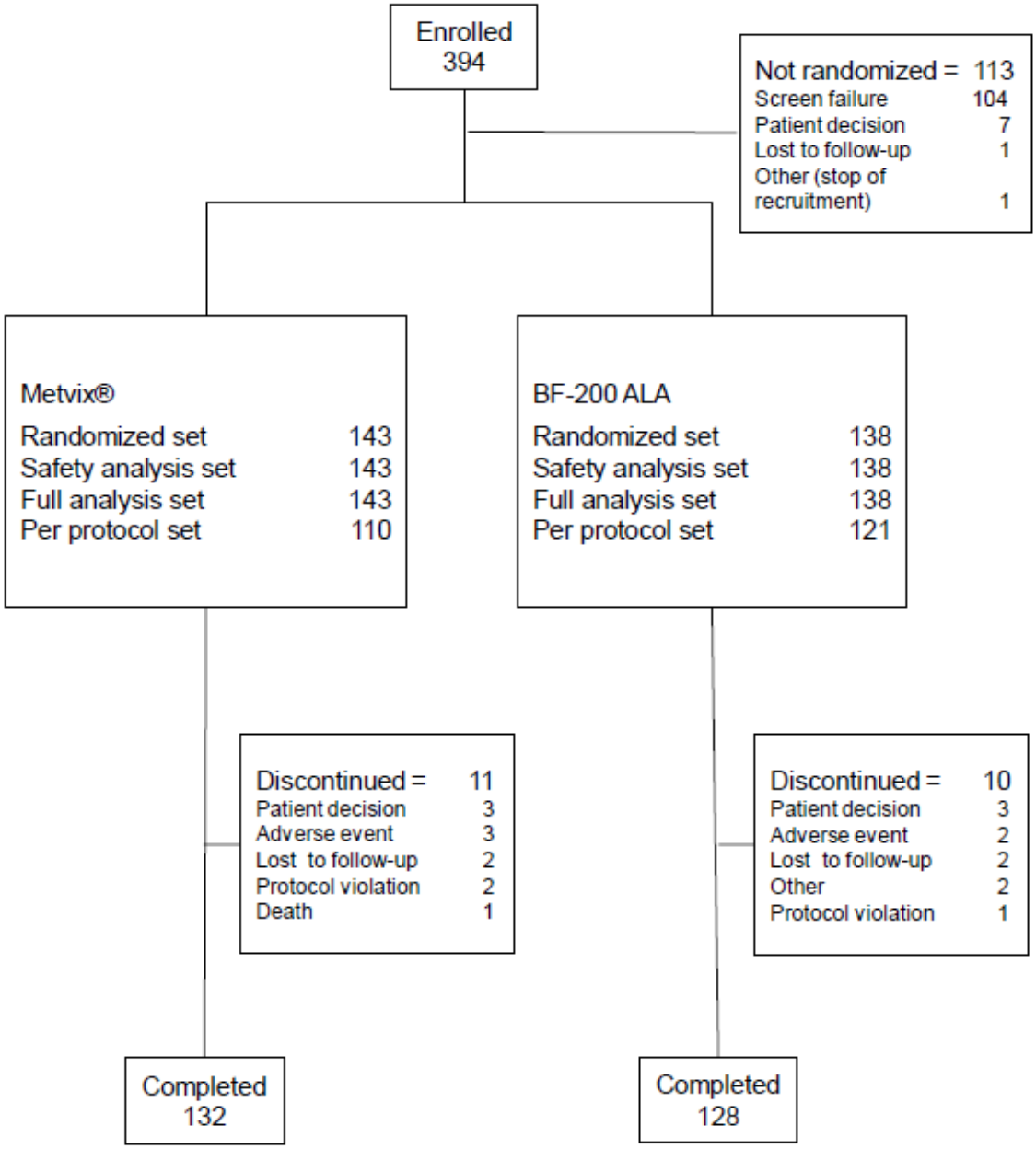
In addition, the corresponding one-sided 97.5% - CIs for the difference in response rates rALA – rMetvix will be presented. Rejection of the primary null hypothesis implies that the lower bound of this CI is greater or equal - Δ. If the lower bound of this CI is greater than 0, BF-200 ALA will be considered superior to Metvix.

The primary analysis will be performed on the PP set.

[9] Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Statistics in medicine. 1990;9(12):1447-54.

Results

Participant flow



Recruitment

The study ALA-BCC-CT008 recruited patients in 24 centres in Germany (20) and UK (4). The recruitment period was approximately 4 months, with the planned first patient in: January 2014 and last patient in approximately in May 2014. The last patient out (observer blind part) was in November 2014 with an expected follow-up until August 2019.

Conduct of the study

In total, 50 patients included in the FAS had at least one major protocol deviation and were excluded from the PP population. Major protocol deviations are summarized by treatment group and overall in Table 2.

Table 2: Major protocol deviations - FAS

Protocol deviation	Number of patients, n (%)					
	Metvix® N=143		BF-200 ALA N=138		Total N=281	
At least one major protocol deviation	33	(23.1)	17	(12.3)	50	(17.8)
No final assessment available at least 8 weeks after last PDT	12	(8.4)	7	(5.1)	19	(6.8)
Prohibited concomitant medication	10	(7.0)	6	(4.3)	16	(5.7)
Delay in scheduled time frame within PDT cycles[a]	12	(8.4)	0	-	12	(4.3)
In/exclusion criteria violated	5	(3.5)	5	(3.6)	10	(3.6)
Mean illumination distance too big	4	(2.8)	1	(0.7)	5	(1.8)
Incubation time less than 2 h	2	(1.4)	1	(0.7)	3	(1.1)
Same tube was used at all 4 PDTs	1	(0.7)	1	(0.7)	2	(0.7)
Non-aggressive subtype of BCC not confirmed by biopsy at screening	1	(0.7)	1	(0.7)	2	(0.7)
No BCC lesion assessment available after PDT-2	1	(0.7)	1	(0.7)	2	(0.7)
Not treated according to randomization schedule	1	(0.7)	0	-	1	(0.4)
Treated lesion is not non-aggressive BCC of appropriate size, thickness, and location at baseline	1	(0.7)	0	-	1	(0.4)

Note: A patient could have more than one protocol deviation. After database closure, it was determined that Patients 108-24 and 111-32 had both received expired medication (Metvix®); both patients were already excluded from the PP set due to other protocol violations.

BCC: basal cell carcinoma; PDT: photodynamic therapy; PP: per-protocol.

Change to the inclusion criterion regarding primary disease eligibility:

Previous to this amendment, patients with any lesions biopsied at screening and assessed as non-eligible according to biopsy results were not allowed to be included into the study, even if eligible lesions existed (an exclusion criterion was “confirmed histopathological diagnosis of other than non-aggressive BCC”). After implementation of this amendment, patients with these non-eligible lesions were allowed to be included if at least one of the lesions was an eligible BCC. The non-eligible lesions had to be at least 10 cm away from the nearest BCC lesion treated within the study and had to be removed surgically. This change was implemented to improve recruitment.

Change to the sample size and number of patients to be included in the study:

This amendment reduced the sample size from a total of 360 patients to a total of 272 patients because a higher overall response than originally anticipated was observed during the blinded monitoring of the study. A higher response rate of between 84 and 90% for the FAS and PP sets was observed with a non-inferiority margin of 15%, respectively, versus an originally anticipated response rate of 80%.

Baseline data

The following table provide a description of demographic characteristics, history of skin cancer and skin type, history of skin diseases treated with non-surgical therapy, history of surgical therapy for skin diseases, disease history and BCC lesion characteristics at baseline.

Table 3: Demographic characteristics - PP analysis set

Characteristic	Number of patients, n (%)					
	Metvix® N=110		BF-200 ALA N=121		Total N=231	
Sex, n (%)						
Male	55	(50.0)	76	(62.8)	131	(56.7)
Female	55	(50.0)	45	(37.2)	100	(43.3)
Age						
Mean (SD)	66.5 (11.53)		67.3 (11.59)		66.9 (11.54)	
Median (Min-Max)	70.0 (31–86)		70.0 (32–94)		70.0 (31–94)	
Age group (years), n (%)						
≥18 - <65	39	(35.5)	44	(36.4)	83	(35.9)
≥65 - <75	44	(40.0)	41	(33.9)	85	(36.8)
≥75	27	(24.5)	36	(29.8)	63	(27.3)
Race, n (%)						
White	110	(100.0)	121	(100.0)	231	(100.0)
Ethnicity, n (%)						
Hispanic or Latino	1	(0.9)	0	-	1	(0.4)
Not Hispanic or Latino	109	(99.1)	121	(100.0)	230	(99.6)
Weight (kg)						
Mean (SD)	78.9 (15.15)		76.6 (13.39)		77.8 (14.28)	
Median (Min-Max)	78.5 (54-134)		76.3 (45-112)		77.4 (45-134)	
Height (cm)						
Mean (SD)	171.7 (8.53)		172.0 (9.26)		171.8 (8.89)	
Median (Min-Max)	172.0 (150-192)		172.0 (150-200)		172.0 (150-200)	
BMI (kg/m^2)						
Mean (SD)	26.68 (4.217)		25.85 (3.778)		26.25 (4.010)	
Median (Min-Max)	26.29 (19.6-41.7)		25.46 (18.0-38.7)		25.70 (18.0-41.7)	

BMI: body mass index; Max: maximum; Min: minimum; n: number of patients; N: number of patients in a treatment group; SD: standard deviation.

Table 4: History of skin cancer and skin type at baseline - PP analysis set

Variable	Number of patients, n (%)					
	Metvix® N=110		BF-200 ALA N=121		Total N=231	
Family history of skin cancer						
No family history	87	(79.1)	99	(81.8)	186	(80.5)
BCC	15	(13.6)	12	(9.9)	27	(11.7)
Skin cancer (not specified)	2	(1.8)	9	(7.4)	11	(4.8)
Melanoma	2	(1.8)	2	(1.7)	4	(1.7)
Other	3	(2.7)	0	–	3	(1.3)
SCC of skin	2	(1.8)	0	–	2	(0.9)
Fitzpatrick Skin Typing Score						
I (0-7)	1	(0.9)	5	(4.1)	6	(2.6)
II (8-16)	46	(41.8)	49	(40.5)	95	(41.1)
III (17-24)	51	(46.4)	55	(45.5)	106	(45.9)
IV (25-30)	11	(10.0)	11	(9.1)	22	(9.5)
V to VI (>30)	1	(0.9)	1	(0.8)	2	(0.9)
I to III (0–24)	98	(89.1)	109	(90.1)	207	(89.6)
IV to VI (≥25)	12	(10.9)	12	(9.9)	24	(10.4)

BCC: basal cell carcinoma; SCC: squamous cell carcinoma.

Table 5: History of skin diseases treated with non-surgical therapy in ≥5 patients - PP analysis set

Skin disease	Number of patients, n (%)					
	Metvix® N=110		BF-200 ALA N=121		Total N=231	
None	41	(37.3)	41	(33.9)	82	(35.5)
actinic keratosis	44	(40.0)	55	(45.5)	99	(42.9)
melanocytic naevus	14	(12.7)	15	(12.4)	29	(12.6)
seborrheic keratosis	11	(10.0)	16	(13.2)	27	(11.7)
Bowen's disease	11	(10.0)	11	(9.1)	22	(9.5)
malignant melanoma	3	(2.7)	10	(8.3)	13	(5.6)
rosacea	5	(4.5)	6	(5.0)	11	(4.8)
SCC of skin	3	(2.7)	4	(3.3)	7	(3.0)
psoriasis	4	(3.6)	2	(1.7)	6	(2.6)
dermatitis	4	(3.6)	1	(0.8)	5	(2.2)

SCC: squamous cell carcinoma.

Table 6: History of surgical therapy for skin disease in ≥2 patients - PP analysis set

Surgical therapy	Number of patients, n (%)					
	Metvix® N=110		BF-200 ALA N=121		Total N=231	
None	79	(71.8)	83	(68.6)	162	(70.1)
skin neoplasm excision	19	(17.3)	27	(22.3)	46	(19.9)
skin lesion excision	14	(12.7)	13	(10.7)	27	(11.7)
cancer surgery	1	(0.9)	5	(4.1)	6	(2.6)
biopsy skin	0	–	2	(1.7)	2	(0.9)
lipoma excision	1	(0.9)	1	(0.8)	2	(0.9)
papilloma excision	1	(0.9)	1	(0.8)	2	(0.9)
skin operation	1	(0.9)	1	(0.8)	2	(0.9)

Table 7: Disease history and BCC lesion characteristics at baseline - PP analysis set

Variable	Number of patients, n (%)					
	Metvix® N=110		BF-200 ALA N=121		Total N=231	
Years since first diagnosis of BCC						
Mean (SD)	4.4 (8.09)		3.8 (6.27)		4.1 (7.19)	
Median (Min-Max)	0.3 (0–55)		0.2 (0–45)		0.2 (0–55)	
History of BCC therapy						
No previous therapy	53	(48.2)	60	(49.6)	113	(48.9)
Non-surgical therapy	1	(0.9)	7	(5.8)	8	(3.5)
Surgical therapy	42	(38.2)	41	(33.9)	83	(35.9)
Non-surgical and surgical therapy	14	(12.7)	13	(10.7)	27	(11.7)
Histological confirmation of BCC						
Only nodular	21	(19.1)	21	(17.4)	42	(18.2)
Only superficial	83	(75.5)	95	(78.5)	178	(77.1)
Others	6	(5.5)	5	(4.1)	11	(4.8)
mixed differentiation	0	–	1	(0.8)	1	(0.4)
nodular, superficial	5	(4.5)	4	(3.3)	9	(3.9)
others	1	(0.9)	0	–	1	(0.4)

Table 8: Number, location and thickness of BCC lesions overall and number and thickness of BCC lesions per patient at baseline - PP analysis set

Variable	Number of lesions, n (%)					
	Metvix® N=110		BF-200 ALA N=121		Total N=231	
Number of BCC lesions overall, n (%)	127	(100.0)	148	(100.0)	275	(100.0)
Location of BCC lesions overall						
Treatment area A (face/forehead)	16	(12.6)	17	(11.5)	33	(12.0)
Treatment area B (bald scalp)	1	(0.8)	0	–	1	(0.4)
Treatment area C (neck/trunk)	87	(68.5)	97	(65.5)	184	(66.9)
Treatment area D (extremities)	23	(18.1)	34	(23.0)	57	(20.7)
Thickness of BCC lesions (mm) overall, n	127		148		275	
Mean (SD)	0.46 (0.363)		0.41 (0.324)		0.44 (0.343)	
Median (Min-Max)	0.34 (0.1–2.0)		0.31 (0.1–1.6)		0.31 (0.1–2.0)	
Number of BCC lesions per patient						
Mean (SD)	1.2 (0.39)		1.2 (0.49)		1.2 (0.45)	
Median (Min-Max)	1.0 (1–3)		1.0 (1–3)		1.0 (1–3)	
Thickness of BCC lesions (mm) per patient						
Mean (SD)	0.48 (0.378)		0.44 (0.344)		0.46 (0.360)	
Median (Min-Max)	0.35 (0.1–2.0)		0.32 (0.1–1.6)		0.33 (0.1–2.0)	

BCC: basal cell carcinoma; Max: maximum; Min: minimum; N: number of patients in a treatment group; n: number of lesions available, SD: standard deviation.

Numbers analysed

The primary analysis was performed on the per-protocol (PP) analysis set and results for the full analysis set (FAS) are presented as supportive analyses (Table 9).

Table 9: Number of patients by analysis set

Population	Number of patients, n (%)					
	Metvix® N=143		BF-200 ALA N=138		Total N=281	
Randomized set	143	(100.0)	138	(100.0)	281	(100.0)
Safety analysis set	143	(100.0)	138	(100.0)	281	(100.0)
Full analysis set	143	(100.0)	138	(100.0)	281	(100.0)
Per-protocol analysis set	110	(76.9)	121	(87.7)	231	(82.2)

Outcomes and estimation

The following tables summarise the efficacy results from the main studies supporting the present application.

Primary endpoint

Table 10: Overall patient complete response rate 12 weeks after the last PDT – PP analysis set

	Number of patients, n (%)	
	Metvix® N=110	BF-200 ALA N=121
Responder, n (%)	101 (91.8)	113 (93.4)
95% two-sided CI[a]	84.6; 96.0	87.0; 96.9
Difference in % points to BF-200 ALA	1.6	
97.5% one-sided CI[b]	-6.5	
p-value[b]	<.0001	
Odds ratio	1.26	
97.5% one-sided CI	0.47	

CI: confidence interval; N: number of patients; n: number of responders.
a Continuity-corrected Wilson CIs.
b Farrington and Manning (non-inferiority test), lower bound.

Secondary endpoint: Lesion complete response

Table 11: Overall lesion complete response rate 12 weeks after the last PDT – PP analysis set

	Number of lesions, n (%)	
	Metvix® N=127	**BF-200 ALA N=148**
Responder, n (%)	118 (92.9)	140 (94.6)
95% two-sided CI[a]	86.6; 96.5	89.3; 97.5
Difference in % points to BF-200 ALA	1.7	
95% two-sided CI[b]	-4.7; 8.6	
Maximum likelihood estimate[c]	1.0050	
95% two-sided CI[c]	0.9403; 1.0742	
p-value[c]	0.8824	

BCC: basal cell carcinoma; CI: confidence interval; N: number of lesions; n: number of lesions that responded.

a Continuity-corrected Wilson CIs.

b Newcombe CIs.

c Negative binomial regression with treatment included as factor and number of BCC lesions at baseline as covariate.

Secondary endpoints

Table 12: Mean size and changes in total lesion area 12 weeks after the last PDT compared to baseline – PP analysis set

Total lesion area	Mean (SD)		p-value*
	Metvix® N=110	**BF-200 ALA N=121**	
Size (mm^2) at baseline	137.5 (80.56)	149.8 (124.41)	-
Size (mm^2) 12 weeks after last PDT	4.1 (19.87)	5.0 (27.20)	0.6978
Percentage change	–97.0 (13.37)	–94.5 (35.07)	-

Note: Missing data were replaced by the last available observation that allowed an assessment of the outcome.

ANCOVA: analysis of covariance; N: number of patients; SD: standard deviation.

* estimated p-value for treatment from ANCOVA model.

Table 13: Overall patient complete response rate 12 weeks after PDT-2 (PDT cycle 1) – PP analysis set

	Number of patients, n (%)	
	Metvix® N=110	**BF-200 ALA N=121**
Responder, n (%)	62 (56.4)	70 (57.9)
95% two-sided CI[a]	46.6; 65.7	48.5; 66.7
Difference in % points to BF-200 ALA	1.5	
95% two-sided CI[b]	-11.7; 14.6	
Odds ratio	1.06	
95% two-sided CI	0.63; 1.79	
p-value[c]	0.9243	

CI: confidence interval; N: number of patients; n: number of responders.
a Continuity-corrected Wilson CIs.
b Continuity-corrected Newcombe CIs.
c p-value from Pearson's chi-square test with Yates' continuity correction.

Table 14: Cosmetic outcome 12 weeks after last PDT – PP analysis set

Outcome	Patients with sum score at baseline of 0 to 3		Patients with sum score at baseline of 1 to 3 (0 excluded)	
	Metvix® N=109	BF-200 ALA N=120	Metvix® N=74[a]	BF-200 ALA N=70[a]
Very good or good, n (%)	36 (33.0)	42 (35.0)	36 (48.6)	42 (60.0)
95% CI[b]	24.5; 42.8	26.7; 44.3	37.0; 60.5	47.6; 71.3
Difference in % points to BF-200 ALA	2.0		11.4	
95% CI[c]	-10.8; 14.6		-5.8; 27.6	
Probabilistic index[d]	0.544		0.583	
95% CI	0.469; 0.620		0.489; 0.678	
p-value	0.2323		0.0745	
Very good, n (%)	16 (14.7)	28 (23.3)	16 (21.6)	28 (40.0)
95% CI[b]	8.9; 23.0	16.3; 32.1	13.2; 33.0	28.7; 52.4
Good, n (%)	20 (18.3)	14 (11.7)	20 (27.0)	14 (20.0)
95% CI[b]	11.8; 27.2	6.8; 19.1	17.7; 38.8	11.7; 31.6
Satisfactory, n (%)	32 (29.4)	43 (35.8)	24 (32.4)	16 (22.9)
95% CI[b]	21.2; 39.0	27.4; 45.2	22.3; 44.4	14.0; 34.7
Unsatisfactory, n (%)	22 (20.2)	17 (14.2)	9 (12.2)	8 (11.4)
95% CI[b]	13.3; 29.2	8.7; 22.0	6.1; 22.3	5.4; 21.8
Impaired, n (%)	19 (17.4)	18 (15.0)	5 (6.8)	4 (5.7)
95% CI[b]	11.1; 26.1	9.4; 22.9	2.5; 15.7	1.8; 14.7

CI: confidence interval; N: number of patients; n: number of patients with particular cosmetic outcome.
a Number of patients with baseline sum score >0.
b Continuity-corrected Wilson confidence limits
c Continuity-corrected Newcombe confidence limits
d Probability of better outcome (positive number) or worse (negative number) with BF-200 ALA treatment

Tertiary endpoint

Table 15: Lesion complete response 12 weeks after PDT-2 (PDT cycle 1) by lesion subgroups – PP analysis set

Subgroup	Category	Statistic	N (%) lesions	
			Metvix® N=127	BF-200 ALA N=148
BCC subtype at baseline (lesion based)	superficial	n/N (%)	60/98 (61.2)	79/119 (66.4)
		95% CI[a]	50.8; 70.7	57.1; 74.6
	nodular	n/N (%)	12/28 (42.9)	10/28 (35.7)
		95% CI[a]	25.0; 62.6	19.3; 55.9
	mixed differentiation, others	n/N (%)	1/1 (100.0)	1/1 (100.0)
		95% CI[a]	5.5; 100.0	5.5; 100.0
Skin type	I to III	n/N (%)	64/112 (57.1)	78/133 (58.6)
		95% CI[a]	47.4; 66.3	49.8; 67.0
	IV or more	n/N (%)	9/15 (60.0)	12/15 (80.0)
		95% CI[a]	32.9; 82.5	51.4; 94.7
Treatment areas involved (lesion based)	A or B	n/N (%)	9/17 (52.9)	10/17 (58.8)
		95% CI[a]	28.5; 76.1	33.5; 80.6
	C	n/N (%)	51/87 (58.6)	63/97 (64.9)
		95% CI[a]	47.6; 68.9	54.5; 74.2
	D	n/N (%)	13/23 (56.5)	17/34 (50.0)
		95% CI[a]	34.9; 76.1	32.8; 67.2
BCC lesion area at baseline	≤50 mm^2	n/N (%)	9/11 (81.8)	6/10 (60.0)
		95% CI[a]	47.8; 96.8	27.4; 86.3
	>50 mm^2 - ≤100 mm^2	n/N (%)	22/37 (59.5)	31/46 (67.4)
		95% CI[a]	42.2; 74.8	51.9; 80.0
	>100 mm^2 - ≤150 mm^2	n/N (%)	16/28 (57.1)	24/39 (61.5)
		95% CI[a]	37.4; 75.0	44.7; 76.2
	>150 mm^2	n/N (%)	26/51 (51.0)	29/53 (54.7)
		95% CI[a]	36.8; 65.0	40.6; 68.2
Lesion thickness (based on individual lesions)	0.0 - 0.2 mm	n/N (%)	16/27 (59.3)	33/40 (82.5)
		95% CI[a]	39.0; 77.0	66.6; 92.1
	>0.2 - 0.4 mm	n/N (%)	34/51 (66.7)	31/56 (55.4)
		95% CI[a]	52.0; 78.9	41.6; 68.4
	>0.4- 0.6 mm	n/N (%)	11/23 (47.8)	15/23 (65.2)
		95% CI[a]	27.4; 68.9	42.8; 82.8
	>0.6 - 0.8 mm	n/N (%)	6/8 (75.0)	4/9 (44.4)
		95% CI[a]	35.6; 95.5	15.3; 77.3
	>0.8 - 1.0 mm	n/N (%)	4/6 (66.7)	3/9 (33.3)
		95% CI[a]	24.1; 94.0	9.0; 69.1
	>1.0 - 1.5 mm	n/N (%)	2/10 (20.0)	4/10 (40.0)
		95% CI[a]	3.5; 55.8	13.7; 72.6
	>1.5 - 2.0 mm	n/N (%)	0/2 (0.0)	0/1 (0.0)
		95% CI[a]	0.0; 80.2	0.0; 94.5

BCC: basal cell carcinoma; CI: confidence interval; N: number of lesions; n: number of lesions that responded.
a Continuity-corrected Wilson CIs.

Table 16: Size and percentage changes in total lesion area 12 weeks after PDT-2 (PDT cycle 1) compared to baseline – PP analysis set

BCC subtype Statistic	Metvix® N=110	BF-200 ALA N=121
Size (mm²) at baseline		
Mean (SD)	137.5 (80.56)	149.8 (124.41)
Median	112.0	117.0
Min – Max	30 – 380	25 – 927
Size (mm^2) 12 weeks after PDT-2 (PDT cycle 1)		
Mean (SD)	31.6 (62.78)	35.1 (79.24)
Median	0	0
Min – Max	0 – 306	0 – 400
Percentage change		
Mean (SD)	-78.3 (41.03)	-72.4 (108.02)
Median	-100.0	-100.0
Min – Max	-100 – 165	-100 – 1040

Note: Missing data were replaced by the last available observation that allowed an assessment of the outcome.
BCC: basal cell carcinoma; min: minimum; max: maximum; N: number of patients with data; PDT: photodynamic therapy; SD: standard deviation.

Table 17: Improvement in skin quality 12 weeks after the last PDT compared to baseline (baseline evaluation "none" excluded) – PP analysis set

Parameter	Metvix®		BF-200 ALA	
	n/N (%)	CI	n/N (%)	CI
Skin surface (roughness/dryness/scaliness)	49/61 (80.3)	67.8; 89.0	46/58 (79.3)	66.3; 88.4
Hyperpigmentation (independent of texture change or hypopigmentation)	18/26 (69.2)	48.1; 84.9	18/31 (58.1)	39.3; 74.9
Hypopigmentation (independent of texture change or hyperpigmentation)	5/12 (41.7)	16.5; 71.4	11/13 (84.6)	53.7; 97.3
Mottled or irregular pigmentation (both hyper- and hypopigmentation)	11/17 (64.7)	38.6; 84.7	14/24 (58.3)	36.9; 77.2
Degree of scarring (independent of pigmentary changes)	12/19 (63.2)	38.6; 82.8	14/24 (58.3)	36.9; 77.2
Atrophy	4/11 (36.4)	12.4; 68.4	10/14 (71.4)	42.0; 90.4

CI: confidence interval; n: number of patients with improvement from baseline; N: number of patients with data at baseline and 12 weeks after last PDT; PDT: photodynamic therapy.

Table 18: Patient satisfaction 12 weeks after the last PDT – PP analysis set

Outcome	Metvix® (N=110)			BF-200 ALA (N=120)		
	n (%)		95% CI	n (%)		95% CI
Very good or good	94	(85.5)	77.2; 91.2	104	(86.7)	79.0; 92.0
Very good	53	(48.2)	38.6; 57.9	59	(49.2)	40.0; 58.4
Good	41	(37.3)	28.4; 47.1	45	(37.5)	29.0; 46.8
Satisfactory	8	(7.3)	3.4; 14.3	11	(9.2)	4.9; 16.2
Unsatisfactory	4	(3.6)	1.2; 9.6	5	(4.2)	1.5; 9.9
Impaired	0	–	0.0; 4.2	0	–	0.0; 3.9

CI: confidence interval; N: number of patients with available data; n: number of patients with satisfaction/impairment.

Ancillary analyses

Table 19: Overall patient complete response rate 12 weeks after the last PDT – FAS

	Number of patients, n (%)	
	Metvix® N=143	BF-200 ALA N=138
Responder, n (%)	121 (84.6)	124 (89.9)
95% two-sided CI[a]	77.4; 89.9	83.3; 94.1
Difference in % points to BF-200 ALA	5.2	
97.5% one-sided CI[b]	-3.3	
p-value[b]	<.0001	
Odds ratio	1.61	
97.5% one-sided CI	0.79	

CI: confidence interval; N: number of patients; n: number of responders.

a Continuity-corrected Wilson CIs.

b Farrington and Manning (non-inferiority test).

Table 20: Overall patient complete response rate 12 weeks after last PDT by patient subgroups – PP analysis set

Subgroup	Category	Statistic	Metvix®	BF-200 ALA	Difference in % points to BF-200 ALA	p-value[a]
Age (years)	≥18 - <65	n/N (%)	37/39 (94.9)	41/44 (93.2)	-1.7	
		95% CI	81.4; 99.1	80.3; 98.2		
		97.5% CI			-14.1	0.0180
	≥65 - <75	n/N (%)	43/44 (97.7)	41/41 (100.0)	2.3	
		95% CI	86.5; 99.9	89.3; 100.0		
		97.5% CI			-9.4	0.0018
	≥75	n/N (%)	21/27 (77.8)	31/36 (86.1)	8.3	
		95% CI	57.3; 90.6	69.7; 94.8		
		97.5% CI			-10.8	0.0085
Sex	male	n/N (%)	51/55 (92.7)	74/76 (97.4)	4.6	
		95% CI	81.6; 97.6	90.0; 99.5		
		97.5% CI			-5.1	<0.0001
	female	n/N (%)	50/55 (90.9)	39/45 (86.7)	-4.2	
		95% CI	79.3; 96.6	72.5; 94.5		
		97.5% CI			-17.9	0.0620
BCC subtype at baseline	only superficial	n/N (%)	80/83 (96.4)	90/95 (94.7)	-1.6	
		95% CI	89.1; 99.1	87.6; 98.0		
		97.5% CI			-9.7	0.0006
	only nodular	n/N (%)	16/21 (76.2)	18/21 (85.7)	9.5	
		95% CI	52.5; 90.9	62.6; 96.2		
		97.5% CI			-15.2	0.0258
	others	n/N (%)	5/6 (83.3)	5/5 (100.0)	16.7	
		95% CI	36.5; 99.1	46.3; 100.0		
		97.5% CI			-26.5	0.0753
Skin type	I to III	n/N (%)	90/98 (91.8)	101/109 (92.7)	0.8	
		95% CI	84.1; 96.2	85.6; 96.5		
		97.5% CI			-7.7	0.0001
	IV or more	n/N (%)	11/12 (91.7)	12/12 (100.0)	8.3	
		95% CI	59.8; 99.6	69.9; 100.0		
		97.5% CI			-16.3	0.0316

Subgroup	Category	Statistic	Metvix®	BF-200 ALA	Difference in % points to BF-200 ALA	p-value[a]
Treatment areas involved	A or B	n/N (%)	10/14 (71.4)	10/13 (76.9)	5.5	
		95% CI	42.0; 90.4	46.0; 93.8		
		97.5% CI			-28.0	0.1152
	C only	n/N (%)	70/73 (95.9)	75/77 (97.4)	1.5	
		95% CI	87.7; 98.9	90.1; 99.5		
		97.5% CI			-7.5	0.0002
	D only	n/N (%)	16/17 (94.1)	18/21 (85.7)	-8.4	
		95% CI	69.2; 99.7	62.6; 96.2		
		97.5% CI			-27.8	0.2527
	Combin-ations[b]	n/N (%)	5/6 (83.3)	10/10 (100.0)	16.7	
		95% CI	36.5; 99.1	65.5; 100.0		
		97.5% CI			-14.4	0.0229
Number of BCCs at baseline	1	n/N (%)	87/94 (92.6)	90/98 (91.8)	-0.7	
		95% CI	84.8; 96.7	84.1; 96.2		
		97.5% CI			-9.6	0.0008
	≥2	n/N (%)	14/16 (87.5)	23/23 (100.0)	12.5	
		95% CI	60.4; 97.8	82.2; 100.0		
		97.5% CI			-6.7	0.0025
Baseline Lesion area	≤50 mm^2	n/N (%)	10/11 (90.9)	8/10 (80.0)	-10.9	
		95% CI	57.1; 99.5	44.2; 96.5		
		97.5% CI			-41.5	0.3966
	>50 mm^2 - ≤100 mm^2	n/N (%)	34/36 (94.4)	43/45 (95.6)	1.1	
		95% CI	80.0; 99.0	83.6; 99.2		
		97.5% CI			-11.2	0.0051
	>100 mm^2 - ≤150 mm^2	n/N (%)	25/26 (96.2)	29/31 (93.5)	-2.6	
		95% CI	78.4; 99.8	77.2; 98.9		
		97.5% CI			-16.9	0.0449
	>150 mm^2	n/N (%)	32/37 (86.5)	33/35 (94.3)	7.8	
		95% CI	70.4; 94.9	79.5; 99.0		
		97.5% CI			-8.4	0.0028

Note: 95% CIs are continuity-corrected Wilson confidence limits, and 97.5% CIs are Farrington and Manning (non-inferiority test).

BCC: basal cell carcinoma; CI: confidence interval; N: number of patients; n: number of responders.

a Farrington and Manning non-inferiority test on a significance level of 2.5% (0.025, one-sided).

b Combinations of treatment areas involved are A+C, A+D, B+C, B+D, C+D.

Table 21: Lesion complete response 12 weeks after last PDT by subgroup – PP analysis set

Subgroup	Category	Statistic	N (%) lesions	
			Metvix® N=127	BF-200 ALA N=148
BCC subtype at baseline (lesion based)	superficial	n/N (%)	95/98 (96.9)	114/119 (95.8)
		95% CI[a]	90.7; 99.2	90.0; 98.4
	nodular	n/N (%)	22/28 (78.6)	25/28 (89.3)
		95% CI[a]	58.5; 91.0	70.6; 97.2
	mixed differentiation, others	n/N (%)	1/1 (100.0)	1/1 (100.0)
		95% CI[a]	5.5; 100.0	5.5; 100.0
Skin type	I to III	n/N (%)	104/112 (92.9)	125/133 (94.0)
		95% CI[a]	86.0; 96.6	88.1; 97.2
	IV or more	n/N (%)	14/15 (93.3)	15/15 (100.0)
		95% CI[a]	66.0; 99.7	74.7; 100.0
Treatment areas involved (lesion based)	A or B	n/N (%)	12/17 (70.6)	14/17 (82.4)
		95% CI[a]	44.0; 88.6	55.8; 95.3
	C	n/N (%)	84/87 (96.6)	95/97 (97.9)
		95% CI[a]	89.5; 99.1	92.0; 99.6
	D	n/N (%)	22/23 (95.7)	31/34 (91.2)
		95% CI[a]	76.0; 99.8	75.2; 97.7
BCC lesion area at baseline	≤50 mm^2	n/N (%)	10/11 (90.9)	8/10 (80.0)
		95% CI[a]	57.1; 99.5	44.2; 96.5
	>50 mm^2 - ≤100 mm^2	n/N (%)	35/37 (94.6)	44/46 (95.7)
		95% CI[a]	80.5; 99.1	84.0; 99.2
	>100 mm^2 - ≤150 mm^2	n/N (%)	27/28 (96.4)	37/39 (94.9)
		95% CI[a]	79.8; 99.8	81.4; 99.1
	>150 mm^2	n/N (%)	46/51 (90.2)	51/53 (96.2)
		95% CI[a]	77.8; 96.3	85.9; 99.3

Subgroup	Category	Statistic	N (%) lesions	
			Metvix® N=127	BF-200 ALA N=148
Lesion thickness (based on individual lesions)	0.0 - 0.2 mm	n/N (%)	27/27 (100.0)	39/40 (97.5)
		95% CI[a]	84.5; 100.0	85.3; 99.9
	>0.2 - 0.4 mm	n/N (%)	50/51 (98.0)	53/56 (94.6)
		95% CI[a]	88.2; 99.9	84.2; 98.6
	>0.4- 0.6 mm	n/N (%)	20/23 (87.0)	23/23 (100.0)
		95% CI[a]	65.3; 96.6	82.2; 100.0
	>0.6 - 0.8 mm	n/N (%)	7/8 (87.5)	9/9 (100.0)
		95% CI[a]	46.7; 99.3	62.9; 100.0
	>0.8 - 1.0 mm	n/N (%)	6/6 (100.0)	8/9 (88.9)
		95% CI[a]	51.7; 100.0	50.7; 99.4
	>1.0 - 1.5 mm	n/N (%)	7/10 (70.0)	8/10 (80.0)
		95% CI[a]	35.4; 91.9	44.2; 96.5
	>1.5 - 2.0 mm	n/N (%)	1/2 (50.0)	0/1 (0.0)
		95% CI[a]	2.7; 97.3	0.0; 94.5

BCC: basal cell carcinoma; CI: confidence interval; N: number of lesions; n: number of lesions that responded.
a Continuity-corrected Wilson CIs

Table 22: Mean percentage changes from baseline in total lesion area 12 weeks after last PDT by BCC subtype – PP analysis set

BCC subtype	Metvix®			BF-200 ALA			Treatment p-value[a]	Baseline lesion area p-value[a]
	n	Mean	SD	n	Mean	SD		
Only superficial	83	-99.4	3.16	95	-93.6	39.39[b]	0.4840	0.3538
Only nodular	21	-86.7	28.20	21	-97.2	8.25	0.2835	0.9846
Others	6	-99.6	0.99	5	-100.0	0	0.3153	0.3798

ANCOVA: analysis of covariance; BCC: basal cell carcinoma; n: number of patients with data; SD: standard deviation.

a ANCOVA with factor treatment and baseline total lesion area as covariate. Missing data were replaced by the last available observation that allowed an assessment of the outcome.

b SD higher due to Patient 201-06, who had an increased lesion area from baseline of 63 mm to 225 mm 12 weeks after the last PDT. This lesion area included a lesion later confirmed to be the benign skin condition lentigo solaris.

Table 23: Overall complete responder rates by subgroup categories

Subgroup	BF-200 ALA Patient number n (%)	BF-200 ALA Full patient clearance in subgroup n (%)	BF-200 ALA Full lesion clearance in subgroup n (%)	Metvix Patient number n (%)	Metvix Full patient clearance in subgroup n (%)	Metvix Full lesion clearance in subgroup n (%)
Patients with more than 1 BCC	23/121 (19.0)	23/23 (100.0)	n.a.	16/110 (14.5)	14/16 (87.5)	n.a.
Superficial (only)	95/121 (78.5)	90/95 (94.7)	114/119 (95.8)	83/110 (75.5)	80/83 (96.4)	95/98 (96.9)
Nodular (only)	21/121 (17.4)	18/21 (85.7)	25/28 (89.3)	21/110 (19.1)	16/21 (76.2)	22/28 (78.6)
Others (including mixed s/nBCCs)	5/121 (4.1)	5/5 (100.0)	1/1 (100.0)	6/110 (5.5)	5/6 (83.3)	1/1 (100.0)
>1mm	n.a.	n.a.	8/11 (72.7)	n.a.	n.a.	8/12 (66.7)
BCC on the head (only)	13/121 (10.7)	10/13 (76.9)	14/17 (82.4)	14/110 (12.7)	10/14 (71.4)	12/17 (70.6)
BCC on the trunk (only)	77/121 (63.6)	75/77 (97.4)	95/97 (97.9)	73/110 (66.4)	70/73 (95.9)	84/87 (96.6)

Patient distribution in the subgroups was similar for both products and represents the distribution in the general population, where more than 70% of BCCs are located in the head/trunk region. BCCs located in this region mainly belong to the superficial subtype. In conclusion, even though subgroup sizes are too small to draw significant conclusions on individual groups, the distribution of the two products to the relevant subgroups is very similar. Thus, it seems not plausible that this could negatively impact the non-inferiority claim of the primary study endpoint or the general trends observed across all subgroups.

Analysis of 6-month Follow-up Results

Patient disposition and demography

Of 260 patients in the FAS (132 in the Metvix group, 128 in the BF-200 ALA group) who completed the clinical part, 242 entered the FU phase [122 (88.4%) in the BF-200 ALA group and 120 (83.9%) in the Metvix group]. All BF-200 ALA treated patients (122 [88.4%]) and 117 (81.8%) Metvix treated patients completed the FU1 period 6 months after the last PDT. 3 patients in the Metvix group dropped out from FU1 prematurely (2 patients were lost to FU, 1 patient decided to discontinue). The corresponding number of lesions entering the FU was 289, of which 239 lesions were superficial at baseline, 48 nodular, and 2 lesions belonged to the mixed differentiation/others subtype. Of the 289 lesions, 282 were completely cleared 12

weeks after the last PDT: 150 lesions in the BF-200 ALA group and 132 in the Metvix group.

Efficacy analysis

Of patients in the BF-200 ALA group with data who were complete responders 12 weeks after the last PDT, 4 (3.3%; 95% CI 1.1; 8.7) were recurrent at the 6-month FU1. Of 114 complete responders with data in the Metvix group, 5 patients relapsed (4.4%; 95% CI 1.6; 10.4) until the 6-month FU1. In the PP analysis set 113 patients with data in the BF-200 ALA group and 99 in the Metvix group were complete responders and entered 6-months FU 12 weeks after the last PDT. Of these patients, 4 (3.5%) were recurrent in the BF-200 ALA group and 5 (5.1%) in the Metvix group.

At the 6-month follow-up visit lesion recurrence rates were low in both treatment groups, with 2.9% and 4.3% in the PPSFU of the BF-200 ALA and Metvix groups, respectively. In the FASFU, similar recurrence rates were observed for both applications. With respect to the different lesion subgroups, lower recurrence rates were obtained in the BF-200 ALA group compared to Metvix for superficial BCC (1.8% vs. 4.3%), for BCCs in the treatment area neck/trunk (3.2% vs 4.9%) and extremities (3.2% vs. 4.8%), for lesions with a baseline lesion area between > 50 mm² - ≤ 100 mm² (0% vs 8.6%), and for lesion with a thickness at baseline between >0.4-0.6 mm (0% vs 5.0%) and >0.6-0.8 mm (0% vs 14.3%), respectively. BF-200 ALA showed slightly higher recurrence rates compared to Metvix in lesions with an area between > 100 mm² - ≤ 150 mm² (5.4% vs 4.0%) and >150 mm² (3.9% vs 2.2%), and in lesions with a thickness of >1.0 to 1.5 mm (25% vs 0%), respectively.

Table 24: Population for analysis in 6-month FUP (FU1)

	BF-200 ALA		**Metvix®**		**Total**	
Patient population	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Clinical treatment period						
Randomized set	138	100.0	143	100.0	281	100.0
Safety analysis set	138	100.0	143	100.0	281	100.0
Full analysis set	138	100.0	143	100.0	281	100.0
Major protocol deviations	17	12.3	33	23.1	50	17.8
Per protocol set	121	87.7	110	76.9	231	82.2
Follow-up period 1 (6mFU)						
Safety analysis set (SAF_{FU})	134	97.1	136	95.1	270	96.1
Full analysis set (FAS_{FU})	122	88.4	120	83.9	242	86.1
Major protocol deviations	9	6.5	17	11.9	26	9.3
Per protocol set (PP_{FU})	113	81.9	103	72.0	216	76.9
Lesion population						
Clinical treatment period						
Safety analysis set	166	100.0	164	100.0	330	100.0
Full analysis set	166	100.0	164	100.0	330	100.0
Major protocol deviations	18	10.8	37	22.6	55	16.7
Per protocol set	148	89.2	127	77.4	275	83.3
Follow-up period 1 (6mFU)						
Safety analysis set (SAF_{FU})	162	97.6	157	95.7	319	96.7
Full analysis set (FAS_{FU})	150	90.4	139	84.8	289	87.6
Major protocol deviations	10	6.0	19	11.6	29	8.8
Per protocol set (PP_{FU})	140	84.3	120	73.2	260	78.8

Table 25: Patient recurrence rates in 6-month Follow up (FU1)

	BF-200 ALA		Metvix®	
	N (%)	**95% CI**	**N (%)**	**95% CI**
PPS_{FU}				
Complete responders 12 weeks after the last PDT with data at FU1	113 (100)		99 (100)	
Patients still completely cleared at FU1	109 (96.5)	90.6 - 98.9	94 (94.9)	88.1 - 98.1
Patients with recurrent BCC lesions	4 (3.5)	1.1 - 9.4	5 (5.1)	1.9 - 11.9
FAS_{FU}				
Complete responders 12 weeks after the last PDT with data at FU1	122 (100)		114 (100)	
Patients still completely cleared at FU1	118 (96.7)	91.3 – 98.9	109 (95.6)	89.6 - 98.4
Patients with recurrent BCC lesions	4 (3.3)	1.1 - 8.7	5 (4.4)	1.6 - 10.4

6-month follow-up (FU-1) PPS_{FU}

Table 26: Lesion recurrence rates in Follow up (FASFU and PPFU analysis set, FU1)

	BF-200 ALA		MAL cream	
	N (%)	**95% CI**	**N (%)**	**95% CI**
6-month follow-up (FU-1) PPS_{FU}				
BCC lesions cleared 12 weeks after last PDT with data at FU-1	140 (100)		115 (100)	
BCC lesions still completely cleared at FU-1	136 (97.1)	92.4; 99.1	110 (95.7)	89.7; 98.4
Recurrent BCC lesions at FU1	4 (2.9)	0.9; 7.6	5 (4.3)	1.6; 10.3
12-month follow-up (FU-2) PPS_{FU}				
BCC lesions cleared 12 weeks after with data at FU-2	134 (100)		110 (100)	
BCC lesions still completely cleared at FU-2	125 (93.3)	87.3; 96.7	101 (91.8)	84.6; 96.0
Recurrent BCC lesions (since FU-1)	5 (3.7)	1.4; 8.9	4 (3.6)	1.2; 9.6
Recurrent BCC lesions (FU-1, FU-2)	9 (6.7)	3.3; 12.7	9 (8.2)	4.0; 15.4
6-month follow-up (FU-1) FAS_{FU}				
BCC lesions cleared 12 weeks after last PDT with data at FU-1	150 (100)		132 (100)	
BCC lesions still completely cleared at FU-1	146 (97.3)	92.9; 99.1	127 (96.2)	90.9; 98.6
Recurrent BCC lesions at FU1	4 (2.7)	0.9; 7.1	5 (3.8)	1.4; 9.1
12-month follow-up (FU-2) FAS_{FU}				
BCC lesions cleared 12 weeks after with data at FU-2	144 (100)		124 (100)	
BCC lesions still completely cleared at FU-2	134 (93.1)	87.3; 96.4	115 (92.7)	86.3; 96.4
Recurrent BCC lesions (since FU-1)	6 (4.2)	1.7; 9.2	4 (3.2)	1.0; 8.6
Recurrent BCC lesions (FU-1, FU-2)	10 (6.9)	3.6; 12.7	9 (7.3)	3.6; 13.7

Table 27: Lesion recurrence rate in Follow up – analyses of subgroups (PPFU analysis set, FU1)

	BF-200 ALA		Metvix®	
PPS_{FU}	N (%)	95% CI	N (%)	95% CI
Lesion recurrence rate by BCC subtype at baseline				
Superficial	2/114 (1.8)	0.3 – 6.8	4/92 (4.3)	1.4 – 11.4
Nodular	1/25 (4.0)	0.2 – 22.3	1/22 (4.5)	0.2 – 24.9
Mixed differentiation, Others	1/1 (100)	5.5 - 100	0/1 (0)	0-.0 – 94.5
Lesion based subgroup by treatment area:				
A (Face/ Forehead) or B (Bald Scalp)	0/14 (0)	0.0 - 26.8	0/12 (0)	0.0 - 30.1
C (Neck/Trunk)	3/95 (3.2)	0.8 - 9.6	4/82 (4.9)	1.6 - 12.7
D (Extremities)	1/31 (3.2)	0.2 – 18.5	1/21 (4.8)	0.2 – 25.9
Lesion recurrence rate in follow-up by baseline BCC lesion area				
<= 50 mm E2	0/8 (0)	0.0 – 40.2	0/9 (0)	0.0 – 37.1
> 50 mm E2 - <= 100 mm E2	0/44 (0)	0.0 – 10.0	3/35 (8.6)	2.2 – 24.2
> 100 mm E2 - <= 150 mm E2	2/37 (5.4)	0.9 – 19.5	1/25 (4.0)	0.2 – 22.3
> 150 mm E2	2/51 (3.9)	0.7 – 14.6	1/46 (2.2)	0.1 – 13.0
Lesion recurrence rate in follow-up by lesion thickness at baseline				
0.0-0.2 mm	0/39 (0)	0.0 – 11.2	0/26 (0)	0.0 – 16.0
>0.2-0.4 mm	2/53 (3.8)	0.7 – 14.1	2/48 (4.2)	0.7 – 15.4
>0.4-0.6 mm	0/23 (0)	0.0 – 17.8	1/20 (5.0)	0.3 – 26.9
>0.6-0.8 mm	0/9 (0)	0.0 – 37.1	1/7 (14.3)	0.8 – 58.0
>0.8-1.0 mm	0/8 (0)	0.0 – 40.2	0/6 (0)	0.0 – 48.3
>1.0-1.5 mm	2/8 (25.0)	4.5 – 64.4	0/7 (0)	0.0 – 43.9
>1.5-2.0 mm	-	-	1/1 (100)	5.5 - 100

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. It should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28: Summary of Efficacy for trial ALA-BCC-CT008

Title: A randomized, observer blind, multinational phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) in comparison to Metvix® in the treatment of non-aggressive basal cell carcinoma (BCC) with photodynamic therapy (PDT)		
Study identifier	ALA-BCC-CT008	
Design	Multinational, randomized, positive-controlled, observer blind, parallel-group (1:1 ratio) study divided in 2 parts: an observer blind part consisting of a screening period and a treatment period, and a follow-up (FU) part.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks not applicable 6, 12 , 24, 36, 60 months

Hypothesis	Non-inferiority		
Treatments groups	BF-200 ALA		2 PDT treatments (PDT-1 and PDT-2) approximately 1 week apart. Patients were evaluated 12 weeks after PDT-2 and according to response
	MAL		2 PDT treatments (PDT-1 and PDT-2) approximately 1 week apart. Patients were evaluated 12 weeks after PDT-2 and according to response
Endpoints and definitions	Primary endpoint	None	overall patient complete response rate assessed 12 weeks after the last PDT
	Secondary endpoint	None	Lesion complete response (completely cleared individual lesions) assessed 12 weeks after the last PDT.
	Secondary endpoint	None	Reduction of total lesion area (summation of sizes of all treated lesions) per patient, assessed 12 weeks after the last PDT.
	Secondary endpoint	None	Patient complete response (complete clearance of all treated lesions) assessed 12 weeks after PDT-2.
	Secondary endpoint	None	Overall cosmetic outcome 12 weeks after the last PDT.
	FU variable	None	Patient recurrence rate defined as the number of patients with at least one recurrent lesion during FU after complete clearance 12 weeks after the last PDT.
Database lock	17 Nov 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol		
Descriptive statistics and estimate variability	Treatment group	BF-200 ALA	MAL
	Number of subject	138	143
	Primary endpoint: Patient complete response 12 weeks after the last PDT	113 (93.4%) 95% CI:84.6; 96.0	101 (91.8%) 95%CI:87.0;96.9
	Odds ratio	1.26 97.5% one-sided CI: 0.47	
	Secondary endpoint: Lesion complete response 12 weeks after the last PDT	140/148 (94.6%) Wilson 95% CI:89.6;97.5)	118/127 (92.9%) Wilson 95% CI: 86.6;96.5)
	Maximum likelihood estimate	1.0050 95%CI: 0.94;1.07 p-value=0.8824	

	Secondary endpoint: Reduction of total lesion area 12 weeks after the last PDT (percentage change)	-94.5%	-97.0%
	p-value=	0.6978	
	Secondary endpoint: Patient complete response (complete clearance of all treated lesions) assessed 12 weeks after PDT-2.	62 (56.4%) 95% CI:46.6; 65.7	70 (57.9%) 95% CI: 48.5;66.7
	Odds ratio	1.06 95% CI: 0.63; 1.79 p-value= 0.9243	
	Secondary endpoint: Overall cosmetic outcome 12 weeks after the last PDT. Very good or good:	42 (35.0%) 95% CI: 26.7; 44.3	36 (33.0%) 95% CI: 24.5;42.8
	Probabilistic index 95% CI p-value:	0.544 0.469; 0.620 0.2323	
	FU variable: Patient recurrence rate defined as the number of patients with at least one recurrent lesion during FU after complete clearance 12 weeks after the last PDT.	6.7%	8.2%
	95% CI	3.3;12.7	4.0;15.4

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The trial ALA-BCC-CT008 was a multinational, randomised, positive-controlled, observer blind, parallel-group (1:1 ratio) study divided in 2 parts: an observer blind part consisting of a screening period and a treatment period, and a follow-up (FU) part for a total study duration for each patient of approximately 61 to 64 months. Efficacy and safety of Ameluz for the treatment of basal cell carcinoma (BCC) with a

thickness of <2mm has been evaluated in 281 patients enrolled in a phase III clinical trial. In this study a total of 138 patients were treated with Ameluz. All patients had 1 to 3 BCC lesions on the face/forehead, bald scalp, extremities and/or neck/trunk. In this study, photodynamic therapy with Ameluz was tested for non-inferiority to a cream containing 16% methyl-aminolevulinate (MAL, methyl-[5-amino-4-oxopentanoate]). The red light source provided a narrow spectrum around 635 nm at a light dose of 37 J/cm2 (BF-RhodoLED). The primary endpoint was complete patient clearance 12 weeks after the last photodynamic therapy. The margin for the non-inferiority was a delta of 15% with a significance level of 0.025 (on sided). The non-inferiority margin was derived from an analysis of previous studies and is therefore justified from a statistical perspective. However, there was no evidence provided that the margin can be regarded as clinically relevant as per the guidance on the Guideline on the choice of the non-inferiority margin (EMEA/CPMP/EWP/2158/99). Considering that the difference between the two treatments is small, this does not pose a major issue. The primary analysis was also based on the PP population, which is different than what is recommended in the guideline EMEA/CPMP/EWP/2158/99. As both PP and FAS analysis are similar, this was not raised as a major issue. Therefore, the design of the trial was considered acceptable and no major issues were raised with the conduct of the study.

The baseline characteristics were well balanced and disease characteristics between the two groups were comparable. No relevant differences have been found between the two groups.

Efficacy data and additional analyses

Based on results of overall patient complete response 12-weeks after the last PDT (2 to 4 PDT sessions in total), BF-200 ALA (Ameluz) was non-inferior compared to Metvix in the treatment of thin (≤2 mm thickness), (non-aggressive) BCC with PDT. Patients treated with BF-200 ALA had 93.4% complete response compared with 91.8% for the Metvix treated group. For BCC lesions, overall lesion complete response rate 12 weeks after the last PDT was 94.6% with BF-200 ALA and 92.9% with Metvix. For nodular BCC, 89.3% of the lesions were cleared with BF-200 ALA and 78.6% with Metvix. Patient satisfaction 12 weeks after last PDT was approximately 87% of patients treated with BF-200 ALA compared to 86% for patients treated with Metvix.

In the Phase III study ALA-BCC-CT008 follow up period, there is evidence that the efficacy achieved 12 weeks after the last PDT is maintained during the 6-month follow up period. Recurrence rates in the different subgroups were in most cases slightly lower for BF-200 ALA than for Metvix. Follow-up results of ALA-BCC-CT008 provided evidence for a continuous improvement of skin quality until 6 months after treatment in both treatment groups, particularly for roughness/dryness/scaliness, hyperpigmentation, and mottled or irregular pigmentation.

The proposed wording of the indication would be for a first line indication for treatment of BCC. However, the current dermatological standards and guidelines recommend surgery as the main first line treatment for BCC. In addition, the comparator is currently indicated for second line indication, and is indicated for patients which are unsuitable for other available therapies due to possible treatment related morbidity and poor cosmetic outcome. Therefore, the indication for Ameluz has been aligned with the second line indication for Metvix, but slightly reworded for conciseness.

The MAH was requested to submit data on the follow-up at 12 months. It is acknowledged that the number of discontinuations in both arms for patients who entered the follow up phase (N=122 for BF-200 ALA and N=120 for the Metvix arm) was very low in both, the first 6 months (N=3) and the second 6 months (N=4) follow-up periods. Recurrence rates are comparable for both arms for the Full Analysis Set, as shown by the main analysis with sensitivity analyses, and across subgroups. Clinical efficacy was re-assessed at follow-up visits 6 and 12 months after the last photodynamic therapy. Lesion recurrence rates after 6 and 12 months were 2.9% and 4.3%, respectively, for Ameluz and 6.7% and 8.2% for MAL.

BCC can be distinguished into non-aggressive and aggressive forms by their fundamentally different biological characteristics as well as their size and body localization. The prototypical varieties of BCC related to non-aggressive BCC include primary nodular (nBCC) and superficial BCC (sBCC) or mixed (n/sBCC) types which tend to be less aggressive in general and thus have a good to intermediate prognosis. Clinically and histologically aggressive BCCs are characterized by an infiltrating, sclerosing/morphoeic, micronodular, or metatypical basosquamous pattern. Perivascular or perineural invasion are features associated with the most aggressive tumour forms. Therefore, the term non-aggressive has been replaced by superficial and nodular in the indication and throughout the SmPC. No definite conclusions regarding the quantitative treatment effect of BF-200 ALA on the overall complete responder rates as dependent on the subgroup categories could be drawn due to limited number of patients in some of the subgroup categories. For the vast majority of the lesions in both groups (92.6% in the BF-200 ALA group and 90.6% in the Metvix group), lesion complete response rates of ≥87% were achieved in lesions with a baseline thickness measurement of 0.0 to 1.0 mm. The lesion complete response rates in both groups decreased in lesions with a baseline thickness measurement of >1.0 mm. With only a small number of lesions >1.0 mm included in this study, the section 5.1 of the SmPC has described information on the thickness of the lesions that were part of the inclusion criteria as <2 mm. The lesion thickness has not been included in the indication as it is also not included in the indication of the comparator Metvix. An analysis exploring a potential relationship between patient complete response 12 weeks after the last PDT and lesion thickness at baseline indicated that baseline lesion thickness had a significant influence on patient complete response. Therefore, it has been specified in SmPC section 5.1 that the patients in the trial had an entry criteria that the BCC thickness was <2 mm. The wording “in adults including the elderly” was not accepted. As adults by definition include the elderly this redundancy is unnecessary and should be avoided (the same argument applies to the actinic keratosis indication wording and the BCC indication wording). It is recommended that the response of BCC lesions may be confirmed by histological examination of biopsy material, if considered necessary. Subsequently, close long term clinical monitoring of BCC is recommended, with histology if necessary (SmPC section 4.2).

2.4.3. Conclusions on the clinical efficacy

The efficacy of Ameluz has been demonstrated in a phase III trial which showed that Ameluz is non-inferior to Metvix in terms of overall patient complete response 12-weeks after the last PDT (2 to 4 PDT sessions in total) with 93.4% versus 91.8%, respectively, in patients with superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment. Results of other secondary and tertiary analyses, including mean percentage reduction of total lesion area 12 weeks after the last PDT, patient complete response 12 weeks after PDT-2 (PDT cycle 1), cosmetic outcome, change in skin quality assessments and patient satisfaction, also demonstrated non-inferiority of BF-200 ALA compared to Metvix.

2.5. Clinical safety

Introduction

Of the 281 patients randomized, 21 patients prematurely discontinued the clinical phase of the study due to patient’s decision (6 patients), AEs (5 patients), lost to FU (4 patients), protocol violation (3 patients), other reason (1 patient each due to “absence at V7 and V8” and “treatment stopped due to patient after V4”) and death (1 patient).

Table 29: Disposition, Ala-BCC-CT008 - Safety Analysis Set

Safety Analysis Set	MAL		BF-200 ALA	
	N=143		N=138	
	No. patients	%	No. patients	%
Completed	132	92.3	128	92.8
Discontinued	10*	7.0*	9*	6.5*
Patient's decision	3	2.1	3	2.2
Adverse event	2*	1.4*	1*	0.7*
Lost to follow-up	2	1.4	2	1.4
Protocol deviation	2	1.4	1	0.7
Other reason	0	0	2	1.4
Death	1	0.7	0	0

Safety Analysis Set: all patients treated at least once with the IMP. The assignment of patients to the treatment groups was as actually treated.

Patient exposure

A total of 281 patients were exposed to PDT in the first session of cycle 1 (PDT-1): 138 patients received BF-200 ALA and 143 patients received Metvix. Approximately half of the patients (116 [41.3%]) who completed cycle 1 had lesions that were not completely cleared at Visit 5 and began a second treatment cycle at that visit (PDT-3: 55 [39.9%] patients received BF-200 ALA and 61 [42.7%] patients received Metvix).

Table 30: Number of patients exposed to PDT by session -SAF

	Number (%) of patients					
	Metvix® N=143		BF-200 ALA N=138		Total N=281	
PDT sessions						
PDT-1	143	(100.0)	138	(100.0)	281	(100.0)
PDT-2	142	(99.3)	138	(100.0)	280	(99.6)
PDT-3	61	(42.7)	55	(39.9)	116	(41.3)
PDT-4	60	(42.0)	55	(39.9)	115	(40.9)

The extent of exposure to PDT is summarized by session and number of illumination procedures in Table 31.

Table 31: Extent of exposure by PDT session and number of illumination procedure - SAF

Variable	Statistic	Metvix®		BF-200 ALA		Total	
PDT-1							
Per-protocol							
Prep of BCC lesions for PDT	N (%)	159	(100.0)	159	(100.0)	318	(100.0)
Illumination procedures	N (%)	157	(98.7)	157	(98.7)	314	(98.7)
Interruption of procedure							
Total interrupted procedures	N (%)	1	(0.6)	0	–	1	(0.3)
due to pain	N (%)	1	(0.6)	0	–	1	(0.3)
due to other reason	N (%)	0	–	0	–	0	–
Procedures with pain relief	N (%)	15	(9.4)	16	(10.1)	31	(9.7)
Light intensity reduced	N (%)	3	(1.9)	3	(1.9)	6	(1.9)
Duration of interruption (min)	Mean (SD)	1.0	–	–	–	1.0	–
PDT-2							
Per-protocol							
Prep of BCC lesions for PDT	N (%)	158	(100.0)	159	(100.0)	317	(100.0)
Illumination procedures	N (%)	153	(96.8)	159	(100.0)	312	(98.4)
Interruption of procedure							
Total interrupted procedures	N (%)	1	(0.6)	3	(1.9)	4	(1.3)
due to pain	N (%)	1	(0.6)	3	(1.9)	4	(1.3)
due to other reason	N (%)	0	–	0	–	0	–
Procedures with pain relief	N (%)	17	(10.8)	18	(11.3)	35	(11.0)
Light intensity reduced	N (%)	2	(1.3)	7	(4.4)	9	(2.8)
Duration of interruption (min)	Mean (SD)	90.0	–	1.0	(0.95)	23.3	(44.49)
PDT-3							
Per-protocol							
Prep of BCC lesions for PDT	N (%)	68	(100.0)	60	(100.0)	128	(100.0)
Illumination procedures	N (%)	68	(100.0)	60	(100.0)	128	(100.0)
Interruption of procedure							
Total interrupted procedures	N (%)	1	(1.5)	0	–	1	(0.8)
due to pain	N (%)	1	(1.5)	0	–	1	(0.8)
due to other reason	N (%)	0	–	0	–	0	–
Procedures with pain relief	N (%)	4	(5.9)	3	(5.0)	7	(5.5)
Light intensity reduced	N (%)	0	–	1	(1.7)	1	(0.8)
Duration of interruption (min)	Mean (SD)	10.0	–	–	–	10.0	–
PDT-4							
Per-protocol							
Prep of BCC lesions for PDT	N (%)	66	(100.0)	59	(98.3)	125	(99.2)
Illumination procedures	N (%)	66	(100.0)	59	(98.3)	125	(99.2)
Interruption of procedure							
Total interrupted procedures	N (%)	1	(1.5)	0	–	1	(0.8)
due to pain	N (%)	1	(1.5)	0	–	1	(0.8)
due to other reason	N (%)	0	–	0	–	0	–
Procedures with pain relief	N (%)	7	(10.6)	4	(6.7)	11	(8.7)
Light intensity reduced	N (%)	0	–	1	(1.7)	1	(0.8)
Duration of interruption (min)	Mean (SD)	15.0	–	–	–	15.0	–

BCC: basal cell carcinoma; min: minutes; N: number of illumination procedures; PDT: photodynamic therapy; SD: standard deviation.

Adverse events

TEAEs

The term AE covers any unfavourable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study. The List of Critical Terms (1998 adaptation of WHO Adverse Reaction Terminology Critical Terms List), was used as guidance for AEs that may be considered serious because they are medically important. An SAE is one that occurs at any dose (including overdose) and:

- Results in death.
- Is life-threatening. “Life-threatening” means that the patient was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event.

All patients in both groups reported at least one TEAE. The most common system organ class (SOC) reported was “general disorders and administration site conditions”. Application site pain was the most common individual TEAEs in both groups, reported in 134 (97.1%) patients in the BF-200 ALA group and in 143 (100.0%) patients in the Metvix group.

The frequency of severe TEAEs was slightly higher in the BF-200 ALA group (54 [39.1%] patients) compared to the Metvix group (48 [33.6%] patients).

Table 32: Overview of Treatment Emergent Adverse Events

AE category	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
All TEAEs	143	(100.0)	138	(100.0)
Patients with				
Related TEAEs	143	(100.0)	138	(100.0)
Serious TEAEs	7	(4.9)	3	(2.2)
Related serious TEAEs	0	–	0	–
TEAEs leading to death	1	(0.7)	0	–
Related TEAEs leading to death	0	–	0	–
TEAEs leading to study withdrawal	4	(2.8)	1	(0.7)
Related TEAEs leading to study withdrawal	1	(0.7)	1	(0.7)
TEAEs rated as local skin reactions	130	(90.9)	122	(88.4)
Related TEAEs rated as local skin reactions	130	(90.9)	121	(87.7)
TEAEs rated as discomfort	143	(100.0)	136	(98.6)
Related TEAEs rated as discomfort	143	(100.0)	136	(98.6)
Pain	143	(100.0)	134	(97.1)
Related pain	143	(100.0)	134	(97.1)

Note: Related is defined as possibly, probably, or definitely related to study treatment. A patient may appear in more than one category, but is counted only once in that category.

N: number of patients; TEAE: treatment-emergent adverse event.

Table 33: TEAEs by SOC (occurrence in ≥2 patients in either treatment group)

SOC	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Patients with at least one TEAE	143	(100.0)	138	(100.0)
General disorders and administration site conditions	143	(100.0)	138	(100.0)
Infections and infestations	24	(16.8)	22	(15.9)
Skin and subcutaneous tissue disorders	21	(14.7)	12	(8.7)
Gastrointestinal disorders	3	(2.1)	7	(5.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	13	(9.1)	6	(4.3)
Nervous system disorders	7	(4.9)	6	(4.3)
Musculoskeletal and connective tissue disorders	4	(2.8)	5	(3.6)
Injury, poisoning and procedural complications	5	(3.5)	4	(2.9)
Respiratory, thoracic and mediastinal disorders	2	(1.4)	4	(2.9)
Investigations	1	(0.7)	3	(2.2)
Surgical and medical procedures	2	(1.4)	3	(2.2)
Vascular disorders	5	(3.5)	3	(2.2)
Cardiac disorders	2	(1.4)	1	(0.7)
Eye disorders	2	(1.4)	1	(0.7)
Reproductive system and breast disorders	2	(1.4)	1	(0.7)
Immune system disorders	4	(2.8)	0	–
Ear and labyrinth disorders	3	(2.1)	0	–

Note: Sorted by frequency in the BF-200 ALA group.
N: number of patients; SOC: system organ class; TEAE: treatment-emergent adverse event.

Table 34: TEAEs by PT (occurrence in ≥2 patients in either treatment group)

PT	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Patients with at least one TEAE	143	(100.0)	138	(100.0)
Application site pain	143	(100.0)	134	(97.1)
Application site erythema	126	(88.1)	120	(87.0)
Application site pruritus	49	(34.3)	59	(42.8)
Application site edema	52	(36.4)	42	(30.4)
Application site paresthesia	39	(27.3)	40	(29.0)
Application site scab	41	(28.7)	34	(24.6)
Application site induration	27	(18.9)	32	(23.2)

PT	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Application site discharge	24	(16.8)	24	(17.4)
Application site exfoliation	12	(8.4)	22	(15.9)
Application site erosion	9	(6.3)	18	(13.0)
Nasopharyngitis	10	(7.0)	11	(8.0)
Application site vesicles	11	(7.7)	10	(7.2)
Actinic keratosis	9	(6.3)	5	(3.6)
Headache	6	(4.2)	5	(3.6)
Application site discomfort	5	(3.5)	5	(3.6)
Application site discoloration	8	(5.6)	4	(2.9)
Application site reaction	5	(3.5)	4	(2.9)
Application site hemorrhage	0	–	4	(2.9)
Application site warmth	6	(4.2)	3	(2.2)
Basal cell carcinoma	5	(3.5)	3	(2.2)
Application site ulcer	4	(2.8)	3	(2.2)
Cough	1	(0.7)	3	(2.2)
Hypertension	2	(1.4)	2	(1.4)
Seborrheic dermatitis	2	(1.4)	2	(1.4)
Bronchitis	1	(0.7)	2	(1.4)
Back pain	0	–	2	(1.4)
Gamma-glutamyltransferase increased	0	–	2	(1.4)
Lower respiratory tract infection	0	–	2	(1.4)
Skin disorder	0	–	2	(1.4)
Fatigue	5	(3.5)	1	(0.7)
Skin papilloma	3	(2.1)	1	(0.7)
Bowen's disease	2	(1.4)	1	(0.7)
Diarrhea	2	(1.4)	1	(0.7)
Erythema	2	(1.4)	1	(0.7)
Influenza	2	(1.4)	1	(0.7)
Cystitis	4	(2.8)	0	–
Application site swelling	3	(2.1)	0	–
Arthralgia	2	(1.4)	0	–
Ear infection	2	(1.4)	0	–

PT	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Hypersensitivity	2	(1.4)	0	–
Pruritus	2	(1.4)	0	–
Seasonal allergy	2	(1.4)	0	–
Seborrheic keratosis	2	(1.4)	0	–
Swelling face	2	(1.4)	0	–
Vertigo	2	(1.4)	0	–

Note: Sorted by frequency in the BF-200 ALA group.
N: number of patients; PT: preferred term; TEAE: treatment-emergent adverse event.

Table 35: TEAEs by intensity

Intensity	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Mild	27	(18.9)	20	(14.5)
Moderate	68	(47.6)	64	(46.4)
Severe	48	(33.6)	54	(39.1)

TEAE: treatment-emergent adverse event.

Table 36: TEAEs considered at least possibly related to study treatment by PT (occurrence in ≥ 2 patients in either treatment group)

PT	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Patients with at least one TEAE considered at least possibly related to study treatment	143	(100.0)	138	(100.0)
Application site pain	143	(100.0)	134	(97.1)
Application site erythema	126	(88.1)	120	(87.0)
Application site pruritus	49	(34.3)	59	(42.8)
Application site edema	51	(35.7)	42	(30.4)
Application site paresthesia	39	(27.3)	40	(29.0)
Application site scab	41	(28.7)	34	(24.6)
Application site induration	27	(18.9)	32	(23.2)
Application site discharge	24	(16.8)	23	(16.7)
Application site exfoliation	12	(8.4)	22	(15.9)
Application site erosion	9	(6.3)	18	(13.0)
Application site vesicles	11	(7.7)	10	(7.2)
Application site discomfort	5	(3.5)	5	(3.6)
Application site discoloration	6	(4.2)	4	(2.9)
Application site reaction	5	(3.5)	4	(2.9)
Application site warmth	6	(4.2)	3	(2.2)
Application site ulcer	4	(2.8)	3	(2.2)
Application site hemorrhage	0	–	3	(2.2)
Fatigue	2	(1.4)	1	(0.7)
Headache	2	(1.4)	1	(0.7)
Application site swelling	3	(2.1)	0	–
Pruritus	2	(1.4)	0	–

Note: Sorted by frequency in the BF-200 ALA group.
N: number of patients; PT: preferred term; TEAE: treatment-emergent adverse event.

Table 37: TEAEs considered at least possibly related by intensity

Intensity	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Mild	30	(21.0)	21	(15.2)
Moderate	69	(48.3)	64	(46.4)
Severe	44	(30.8)	53	(38.4)

TEAE: treatment-emergent adverse event.

Table 38: TEAEs rated as discomfort by PT (occurrence in ≥2 patients in either treatment group)

PT	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Patients with at least one TEAE rated as discomfort	143	(100.0)	136	(98.6)
Application site pain	139	(97.2)	127	(92.0)
Application site pruritus	49	(34.3)	59	(42.8)
Application site paresthesia	39	(27.3)	40	(29.0)
Application site discomfort	4	(2.8)	5	(3.6)
Application site reaction	2	(1.4)	4	(2.9)
Application site warmth	6	(4.2)	3	(2.2)
Application site scab	3	(2.1)	1	(0.7)

Note: Sorted by frequency in the BF-200 ALA group.
N: number of patients; PT: preferred term; TEAE: treatment-emergent adverse event.

Table 39: TEAEs rated as discomfort by intensity

Intensity	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Mild	54	(37.8)	45	(32.6)
Moderate	54	(37.8)	54	(39.1)
Severe	35	(24.5)	37	(26.8)

TEAE: treatment-emergent adverse event.

Table 40: TEAEs rated as application site pain by intensity

Intensity	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Mild	38	(26.6)	24	(17.4)
Moderate	63	(44.1)	65	(47.1)
Severe	42	(29.4)	45	(32.6)

TEAE: treatment-emergent adverse event.

Table 41: Investigator assessment of local skin reaction severity

Intensity	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Mild	68	(47.6)	69	(50.0)
Moderate	49	(34.3)	45	(32.6)
Severe	13	(9.1)	8	(5.8)

Table 42: TEAEs rated as local skin reactions by PT (occurrence in ≥2 patients in either treatment group)

PT	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Patients with at least one TEAE rated as local skin reaction	130	(90.9)	122	(88.4)
Application site erythema	126	(88.1)	119	(86.2)
Application site edema	52	(36.4)	42	(30.4)
Application site scab	39	(27.3)	33	(23.9)
Application site induration	27	(18.9)	32	(23.2)
Application site discharge	24	(16.8)	24	(17.4)
Application site exfoliation	12	(8.4)	22	(15.9)
Application site erosion	9	(6.3)	18	(13.0)
Application site vesicles	11	(7.7)	10	(7.2)
Application site discoloration	8	(5.6)	4	(2.9)
Application site hemorrhage	0	–	4	(2.9)
Application site ulcer	4	(2.8)	3	(2.2)
Application site reaction	3	(2.1)	0	–
Application site swelling	2	(1.4)	0	–

Note: Sorted by frequency in the BF-200 ALA group.
N: number of patients; PT: preferred term; TEAE: treatment-emergent adverse event.

Table 43: Serious TEAEs by PT

PT	Number (%) of patients			
	Metvix® N=143		BF-200 ALA N=138	
Patients with at least one serious TEAE	7	(4.9)	3	(2.2)
Basal cell carcinoma	0	–	1	(0.7)
Prostate cancer	0	–	1	(0.7)
Supraventricular tachycardia	0	–	1	(0.7)
Bowen's disease	1	(0.7)	0	–
Colitis	1	(0.7)	0	–
Colitis ulcerative	1	(0.7)	0	–
Coronary artery disease	1	(0.7)	0	–
Death	1	(0.7)	0	–
Glaucoma	1	(0.7)	0	–
Malignant melanoma in situ	1	(0.7)	0	–
Squamous cell carcinoma	1	(0.7)	0	–
Uterine prolapse	1	(0.7)	0	–

Note: Sorted by frequency in the BF-200 ALA group.
N: number of patients; PT: preferred term; TEAE: treatment-emergent adverse event.

Table 44: Investigator's assessment of local skin reaction severity in the overall treatment area by PDT session and most common reaction categories

Variable	Metvix®		95% CIs	BF-200 ALA		95% CIs
PDT-1, n	**n=143**			**n=138**		
Erythema, n (%) none	32	(22.4)	15.8-30.1	26	(18.8)	12.7-26.4
Mild	67	(46.9)	38.5-55.4	83	(60.1)	51.5-68.4
Moderate	38	(26.6)	19.5-34.6	24	(17.4)	11.5-24.8
Severe	5	(3.5)	1.1-8.0	5	(3.6)	1.2-8.3
Edema, n (%) none	109	(76.2)	68.4-82.9	108	(78.3)	70.4-84.8
Mild	19	(13.3)	8.2-20.0	23	(16.7)	10.9-24.0
Moderate	13	(9.1)	4.9-15.0	7	(5.1)	2.1-10.2
Severe	1	(0.7)	0.0-3.8	0	(0.0)	0.0-2.6
Induration, n (%) none	125	(87.4)	80.8-92.4	115	(83.3)	76.0-89.1
Mild	14	(9.8)	5.5-15.9	21	(15.2)	9.7-22.3
Moderate	3	(2.1)	0.4-6.0	2	(1.4)	0.2-5.1
Severe	0	(0.0)	0.0-2.5	0	(0.0)	0.0-2.6

Variable	Metvix®		95% CIs	BF-200 ALA		95% CIs
PDT-2, n	**n=142**			**n=138**		
Erythema, n (%) none	32	(22.5)	16.0-30.3	30	(21.7)	15.2-29.6
Mild	61	(43.0)	34.7-51.5	74	(53.6)	44.9-62.1
Moderate	42	(29.6)	22.2-37.8	31	(22.5)	15.8-30.3
Severe	6	(4.2)	1.6-9.0	3	(2.2)	0.5-6.2
Edema, n (%) none	98	(69.0)	60.7-76.5	108	(78.3)	70.4-84.8
Mild	25	(17.6)	11.7-24.9	17	(12.3)	7.3-19.0
Moderate	17	(12.0)	7.1-18.5	10	(7.2)	3.5-12.9
Severe	1	(0.7)	0.0-3.9	3	(2.2)	0.5-6.2
Induration, n (%) none	124	(87.3)	80.7-92.3	120	(87.0)	80.2-92.1
Mild	13	(9.2)	5.0-15.1	14	(10.1)	5.7-16.4
Moderate	3	(2.1)	0.4-6.0	3	(2.2)	0.5-6.2
Severe	1	(0.7)	0.0-3.9	1	(0.7)	0.0-4.0
PDT-3, n	**n=61**			**n=55**		
Erythema, n (%) none	14	(23.0)	13.2-35.5	11	(20.0)	10.4-33.0
Mild	27	(44.3)	31.5-57.6	29	(52.7)	38.8-66.3
Moderate	17	(27.9)	17.1-40.8	13	(23.6)	13.2-37.0
Severe	3	(4.9)	1.0-13.7	2	(3.6)	0.4-12.5
Edema, n (%) none	45	(73.8)	60.9-84.2	46	(83.6)	71.2-92.2
Mild	8	(13.1)	5.8-24.2	7	(12.7)	5.3-24.5
Moderate	8	(13.1)	5.8-24.2	2	(3.6)	0.4-12.5
Severe	0	(0.0)	0.0-5.9	0	(0.0)	0.0-6.5
Induration, n (%) none	54	(88.5)	77.8-95.3	47	(85.5)	73.3-93.5
Mild	4	(6.6)	1.8-15.9	5	(9.1)	3.0-20.0
Moderate	3	(4.9)	1.0-13.7	3	(5.5)	1.1-15. 1
Severe	0	(0.0)	0.0-5.9	0	(0.0)	0.0-6.5

Variable	Metvix®		95% CIs	BF-200 ALA		95% CIs
PDT-4, n	**n=60**			**n=55**		
Erythema, n (%) none	11	(18.3)	9.5-30.4	9	(16.4)	7.8-28.8
Mild	27	(45.0)	32.1-58.4	27	(49.1)	35.4-62.9
Moderate	19	(31.7)	20.3-45.0	18	(32.7)	20.7-46.7
Severe	3	(5.0)	1.0-13.9	1	(1.8)	0.0-9.7
Edema, n (%) none	50	(83.3)	71.5-91.7	43	(78.2)	65.0-88.2
Mild	6	(10.0)	3.8-20.5	10	(18.2)	9.1-30.9
Moderate	4	(6.7)	1.8-16.2	2	(3.6)	0.4-12.5
Severe	0	(0.0)	0.0-6.0	0	(0.0)	0.0-6.5
Induration, n (%) none	54	(90.0)	79.5-96.2	49	(89.1)	77.8-95.9
Mild	4	(6.7)	1.8-16.2	3	(5.5)	1.1-15.1
Moderate	2	(3.3)	0.4-11.5	3	(5.5)	1.1-15.1
Severe	0	(0.0)	0.0-6.0	0	(0.0)	0.0-6.5

Note: Exact Clopper-Pearson confidence limits are presented. Percentages are based on the numbers of treated patients. If more than one area has been treated, maximum intensity over all areas was used for analysis.

CI: confidence interval; n: number of patients with data available at each PDT session.

A summary of the ADRs reported in patients treated with PDT are presented in Table 45. The data was derived from the Integrated Safety Analysis of AK studies and the BCC study ALA-BCC-CT008 (total 522 patients [384 patients treated with Ameluz in AK pivotal studies and 138 patients treated with Ameluz in BCC studies]).

Table 45: Summary of related adverse drug reactions (ADRs) reported in patients treated with photodynamic therapy with 5-aminolaevulinic acid

System organ class	Frequency	Adverse reaction (preferred terms)	Frequency (%)	Seriousness
Infections and infestations	Uncommon	At application site: Pustules	0.57	Non serious
		Not at application site: Rash pustular	0.38	Non serious
Psychiatric disorders	Uncommon	Nervousness	0.19	Non serious
Nervous system disorders	Common	Headache	1.53	Non serious
	Uncommon	Dysaesthesia	0.19	Non serious
	Not known*	Transient global amnesia (incl. confusion and disorientation)	Post-marketing data. Four cases	Serious
Eye disorders	Uncommon	Eyelid oedema, vision blurred, visual impairment	0.57 0.19 0.19	Non serious Non serious Non serious
Skin and subcutaneous disorders	Uncommon	Blister, dry skin, petechiae	0.38 0.19 0.19	Non serious Non serious Non serious
Musculoskeletal and connective tissue disorders	Uncommon	Back pain	0.19	Non serious

General disorders and administration site conditions	Very common	At application site: Erythema, irritation, pain (incl. burning pain), pruritus, oedema, exfoliation, scab	 84.48 55.36 77.97 31.80 28.35 12.64 15.71	 Non serious Non serious Non serious Non serious Non serious Non serious Non serious
	Common	At application site: Induration, vesicles, paraesthesia, hyperalgesia, erosion, discomfort, discharge	 13.03 7.47 11.30 2.49 4.98 2.30 5.36	 Non serious Non serious Non serious Non serious Non serious Non serious Non serious
	Uncommon	At application site: Haemorrhage, warmth, discoloration, ulcer, swelling, inflammation	 1.34 1.15 0.96 0.57 0.19 0.19	 Non serious Non serious Non serious Non serious Non serious Non serious
		Not at application site: Chills, feeling hot, pyrexia, pain, fatigue	 0.57 0.38 0.38 0.19 0.19	 Non serious Non serious Non serious Non serious Non serious
Injury, poisoning and procedural complications	Uncommon	Wound secretion	0.19	Non serious

Analysis of 6-month Follow-up Results for safety

Of the 281 patients randomized to the study, 270 (96.1%) entered the follow-up period 1 (Safety Analysis Set- SAF), 136 (95.1%) patients in the Metvix group and 134 (97.1%) patients in the BF-200 ALA group. 31 patients in the Metvix group and 28 patients in the BF-200 ALA group experienced at least one post-treatment AE. All AEs were assessed as unrelated or unlikely related, except 1 AE in the Metvix group (recurrent BCC) and 3 AEs in the BF-200 ALA group (recurrent BCC, solar lentigo, and lichenoid keratosis) which are assessed as possibly related.

One AE in the BF-200 ALA group (musculoskeletal discomfort) was erroneously classified as definitely related, and corrected by the investigator to the causality “unrelated” after data base closure. The highest proportion of AEs were reported for the SOC Neoplasms benign, malignant and unspecified (including cysts and polyps), comprising mostly of BCCs (16 in the Metvix group, and 11 in the BF-200 ALA group). BF-200 ALA were recurrent BCCs. Another 5 BCCs in each group occurred outside the treatment area. The majority of untreated/new BCCs was observed in non-naïve patients (9 in the Metvix, 7 in the BF-200 ALA group, respectively). Of the 16 patients with BCC in the Metvix group, 1 patient suffered additionally from SCC, another patient from Bowen’s disease. An event of melanoma had not been reported to the sponsor. Overall, 12 SAEs in 11 patients were reported during the 6-month FU. 10 patients experienced one SAE each (4 patients in the Metvix group and 6 patients the BF-200 ALA group, respectively). One patient in the Metvix group suffered from 2 SAEs. All patients recovered from the SAEs, except 2 patients in the BF-200 ALA group who had an ongoing SAE (angioedema and breast cancer, respectively). All SAEs were assessed as unrelated to the study medication.

Two further SAEs were listed in the BF-200 ALA group, both for unrelated, new BCCs that occurred during the clinical part of the study but were not correctly listed in the CSR. Both had been removed by surgery, resulting in recovery of the patients.

Serious adverse event / deaths / other significant events

Serious TEAEs were lower in the BF-200 ALA (3 [2.2%]) group compared to the Metvix group (7 [4.9%]), all assessed by the investigator as not related to study medication.

According to the AE database, 5 patients (1 patient in the BF-200 ALA group and 4 patients in the Metvix group) had TEAEs that led to study discontinuation. However, 1 of the 4 patients in the Metvix group was erroneously included due to a data entry error at the site. Another patient in the Metvix group died and this event was counted as both a death and an event leading to discontinuation.

Deaths

One patient in the Metvix group died during the observer blind part of the study due to an unknown cause. The investigator and sponsor assessed the event as not related to study medication.

Laboratory findings

Hematology, blood chemistry, and urinalysis data were examined for changes that occurred during treatment and within 12 weeks after discontinuation or completion of patients' last PDT. Laboratory parameters showed no clinically relevant changes.

Table 46: Shift of safety lab parameters from clinical significance aspect in clinical trial ALA-BCC-CT008

Parameter	Metvix						BF-200 ALA					
	Baseline (V1)			12 weeks after PDT (V5 or V8)			Baseline (V1)			12 weeks after PDT (V5 or V8)		
	Normal	Abnormal clin. not signif.	Abnormal clin. signif.	Normal	Abnormal clin. not signif.	Abnormal clin. signif.	Normal	Abnormal clin. not signif.	Abnormal clin. signif.	Normal	Abnormal clin. not signif.	Abnormal clin. signif.
Haematology Parameters												
Haematocrit	102 (88.7)	13 (11.3)	0	102 (88.7)	13 (11.3)	0	106 (90.6)	11 (9.4)	0	103 (88.0)	14 (12.0)	0
Haemoglobin (mmol/L)	102 (88.7)	13 (11.3)	0	106 (92.2)	9 (7.8)	0	105 (89.7)	12 (10.3)	0	105 (89.7)	12 (10.3)	0
Erythrocytes (10E12/L)	97 (84.3)	18 (15.7)	0	93 (80.9)	22 (19.1)	0	93 (79.5)	24 (20.5)	0	96 (82.1)	21 (17.9)	0
Leukocytes (10E9/L)	107 (93.0)	7 (6.1)	1 (0.9)	106 (92.2)	8 (7.0)	1 (0.9)	105 (91.3)	10 (8.7)	0	102 (88.7)	13 (11.3)	0
Neutrophils (10E9/L)*	37 (97.4)	1 (2.6)	0	36 (94.7)	2 (5.3)	0	41 (100)	0	0	39 (95.1)	2 (4.9)	0
Neutrophils/Leukocytes*	60 (84.5)	11 (15.5)	0	61 (85.9)	10 (14.1)	0	61 (82.4)	13 (17.6)	0	62 (83.8)	12 (16.2)	0
Basophils (10E9/L) *	33 (100)	0	0	32 (97.0)	1 (3.0)	0	34 (100)	0	0	34 (100)	0	0
Basophils/Leukocytes*	60 (84.5)	11 (15.5)	0	58 (81.7)	13 (18.3)	0	57 (75.0)	19 (25.0)	0	63 (82.9)	13 (17.1)	0
Lymphocytes (10E9/L) *	32 (84.2)	5 (13.2)	1 (2.6)	29 (76.3)	8 (21.1)	1 (2.6)	33 (80.5)	8 (19.5)	0	34 (82.9)	7 (17.1)	0
Lymphocytes/Leukocyte*s	56 (78.9)	15 (21.1)	0	51 (71.8)	20 (28.2)	0	53 (69.7)	23 (30.3)	0	58 (76.3)	18 (23.7)	0
Monocytes (10E9/L) *	37 (97.4)	1 (2.6)	0	35 (92.1)	2 (5.3)	1 (2.6)	40 (97.6)	1 (2.4)	0	40 (97.6)	1 (2.4)	0
Monocytes/Leukocytes*	58 (81.7)	13 (18.3)	0	59 (83.1)	12 (16.9)	0	64 (84.2)	12 (15.8)	0	65 (85.5)	11 (14.5)	0
Eosinophils (10E9/L) *	36 (100)	0	0	36 (100)	0	0	37 (97.4)	1 (2.6)	0	37 (97.4)	1 (2.6)	0
Eosinophils/Leukocytes*	49 (69.0)	22 (31.0)	0	54 (76.1)	17 (23.9)	0	55 (72.4)	21 (27.6)	0	56 (73.7)	20 (26.3)	0
Platelets (10E9/L)	109 (94.8)	6 (5.2)	0	105 (91.3)	10 (8.7)	0	112 (95.7)	5 (4.3)	0	110 (94.0)	7 (6.0)	0
Serum Chemistry Parameters												
Glucose (mmol/L)	74 (67.3)	36 (32.7)	0	76 (69.1)	34 (30.9)	0	80 (69.6)	35 (30.4)	0	76 (66.1)	39 (33.9)	0
Creatinine (umol/L)	104 (88.9)	13 (11.1)	0	100 (85.5)	17 (14.5)	0	109 (88.6)	13 (10.6)	1 (0.8)	108 (87.8)	14 (11.4)	1 (0.8)
Total Bilirubin (umol/L)	111 (96.5)	4 (3.5)	0	112 (97.4)	3 (2.6)	0	111 (94.1)	7 (5.9)	0	114 (96.6)	4 (3.4)	0
AST (U/L)	105 (94.6)	6 (5.4)	0	106 (95.5)	5 (4.5)	0	112 (96.6)	4 (3.4)	0	113 (97.4)	2 (1.7)	1 (0.9)
ALT (U/L)	109 (93.2)	8 (6.8)	0	110 (94.0)	7 (6.0)	0	119 (97.5)	3 (2.5)	0	117 (95.9)	5 (4.1)	0
LDH (U/L)	81 (77.1)	24 (22.9)	0	82 (78.1)	23 (21.9)	0	95 (84.8)	17 (15.2)	0	94 (83.9)	18 (16.1)	0
AP (U/L)	109 (96.5)	4 (3.5)	0	112 (99.1)	1 (0.9)	0	112 (94.1)	7 (5.9)	0	113 (95.0)	6 (5.0)	0
GGT (U/L)	104 (93.7)	6 (5.4)	1 (0.9)	103 (92.8)	7 (6.3)	1 (0.9)	103 (89.6)	12 (10.4)	0	101 (87.8)	12 (10.4)	2 (1.7)
Potassium (mmol/L)	93 (83.0)	19 (17.0)	0	93 (83.0)	19 (17.0)	0	95 (79.2)	25 (20.8)	0	100 (83.3)	20 (16.7)	0
Sodium (mmol/L)	102 (91.9)	9 (8.1)	0	106 (95.5)	5 (4.5)	0	114 (93.4)	8 (6.6)	0	110 (90.2)	12 (9.8)	0
Calcium (mmol/L)	108 (97.3)	3 (2.7)	0	103 (92.8)	8 (7.2)	0	110 (96.5)	4 (3.5)	0	113 (99.1)	1 (0.9)	0
Total Protein (g/L)	101 (91.8)	9 (8.2)	0	102 (92.7)	8 (7.3)	0	108 (93.1)	8 (6.9)	0	101 (87.1)	15 (12.9)	0
Albumin (g/L)	99 (95.2)	5 (4.8)	0	101 (97.1)	3 (2.9)	0	103 (94.5)	6 (5.5)	0	105 (96.3)	4 (3.7)	0

Safety in special populations

No pregnancies were reported during the study.

Post marketing experience

There is no post marketing experience with the product in the applied indication as it has not been previously approved.

During the post-marketing period, the MAH became aware of one scientific publication referring to 5 individual case reports pertaining to 5 patients who experienced transient memory impairment after PDT. Three of the 5 patient had been treated with ALA (exact product unknown) and 2 have been treated with MAL[10]. Torsnes et al. commented on the publication by Reinholz et al. and provided an additional case report

[10] Reinholz M, Heppt MV, Hoffmann FS, Lummel N, Ruzicka T, Lehmann P, Berking C. Transient memory impairment and transient global amnesia induced by photodynamic therapy. Br J Dermatol. 2015 Nov;173(5):1258-62.

pertaining to a patient who experienced memory impairment after MAL-PDT[11] . No reports on amnesia during PDT were reported from clinical trials.

No further reports pertaining to memory impairment have been reported directly to the MAH until datalock point of a report. However, after data lock one serious case referring to memory impairment was reported. This case was considered serious.

2.5.1. Discussion on clinical safety

The frequency of severe TEAEs was higher in the BF-200 ALA group (54 [39.1%] patients) compared to the Metvix group (48 [33.6%] patients). The most commonly reported TEAEs in both groups were also the most commonly reported related TEAEs, and were TEAEs of the application site (pain, erythema, pruritus, and edema). The most frequent skin reaction observed during PDT in both treatment groups was erythema, which was observed with slightly lower frequency in the BF-200 ALA group compared to the Metvix group. No statistically differences were observed between the two treatment groups in patient reported frequencies and severity rating of local discomfort (characterized as itching, burning, or other discomfort), and local pain. The frequencies of patients with serious TEAEs (all assessed by the investigator as not related to study medication) and TEAEs that led to study discontinuation were low and comparable between the treatment groups.

No other clinically relevant safety concerns were observed during the observer blind part of this study.

From the current indication in AK, the most common signs and symptoms are application site irritation, erythema, pain, and oedema. Most adverse reactions occur during illumination or shortly afterwards. The symptoms are usually of mild or moderate intensity (investigator's assessment on a 4 -point scale), and last for 1 to 4 days in most cases. Following the assessment of the trial CT008 for BCC, new ADRs have been identified which have been included in the section 4.8 of the SmPC. These are vision blurred, visual impairment (frequency as uncommon), burning pain (frequency as very common), inflammation (frequency as uncommon) and back pain (uncommon) were considered related to the treatment. A new ADR, TGA, was observed during the post-marketing period and was assessed during the renewal procedure. The available data on TGA pertain to 2 case report publications (ALA and MAL) and 1 spontaneous case reported to the MAH after DLP of this report but no events were reported in the clinical trial program. Patient and Health Care Professionals should be adequately informed on the risk of memory impairment caused by stress as sometimes occurs during PDT sessions. Therefore, "Transient memory loss and Transient Global Amnesia (TGA)" was added as further potential identified risk to the summary table of safety concerns and as a new ADR in section 4.8 of the SmPC. Routine risk minimisation activities are considered sufficient to monitor this new ADR as the product is applied by health care professionals, who should recognize newly developed neurological and/or psychological.

There were two additional warnings that have been included in the SmPC section 4.4. Following post-marketing experience, TGA has been identified based on literature article. Therefore it has been included as a new ADR and included as an important potential risk as part of the important safety concerns in the RMP as there is not yet enough evidence to include it as an identified risk.

Risk of Transient Global Amnesia (TGA)

Photodynamic therapy (PDT) may be a precipitating factor for transient global amnesia in very rare instances. Although the exact mechanism is not known, stress and pain associated with PDT may increase the risk to develop transient amnesia. If amnesia is observed, the PDT must be discontinued immediately (see section 4.8).

[11] Torsnes LR, Heidenheim M, Jemec GB. Comment on 'Transient memory impairment and transient global amnesia induced by photodynamic therapy'. Br J Dermatol. 2016 Jan;174(1):237.

PDT is usually accompanied by inflammation of the skin, which is regarded as an important response part of the treatment effect with Ameluz. As the exclusion criteria from the clinical trial for BCC, excluded patients that were undergoing immunosuppressant therapy, a new warning has been included to inform the HCP that the use of immunosuppressants during treatment with Ameluz is not recommended (SmPC section 4.4).

Except for TGA, no new important safety concerns have been identified. The important identified risk of application site reaction is included in the SmPC. The important potential risks of application site hypersensitivity, severe application site reaction in combination with photosensitizing medication or in patients with photodermatoses, recurrence rate in treated lesions and conversion into SCC and other types of skin cancer are being managed through routine risk minimisation measures. The concern for off label use has been changed to only include acne and warts as the use in BCC is being approved and is no longer a potential risk. There is still important missing information for the treatment of immunosuppressed patients, safety in patients with skin type I (Fitzpatrick) and safety in pediatric or adolescent patients. The risks are minimised through recommendations in the SmPC and have been included in the RMP. No additional risk minimisation measures are necessary since the product is applied under the supervision of health care professionals experienced in the use of photodynamic therapy who should ensure that the product is used according to the label and would recognise any of the safety concerns described in the PI.

2.5.2. Conclusions on clinical safety

In summary, frequencies and severity of TEAEs are consistent with the ADRS and safety concerns that have been previously evaluated. No new safety concerns were observed during the observer blind part of this study or during the 6 month follow up period. The safety and tolerability of BF-200 ALA in BCC patients is considered acceptable and manageable taking into account the recommendations in the SmPC, risk minimisation measures and through PhV.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 14/06/2018.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and/or CHMP.

The CHMP endorsed the Risk Management Plan version 11 (dated 23 November 2016) which included also changes requested within EMEA/H/C/002204/R/0023 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Table 47: Summary of safety concerns

Important identified risks	Application Site Reaction

Important potential risks	Severe application site reaction in combination with photosensitizing medication or in patients with photodermatoses Application Site Hypersensitivity Transient memory impairment and Transient Global Amnesia (TGA)* Recurrence rate in treated lesions Off-label use ~~in conditions other than AK~~ (e.g. ~~basal cell carcinoma,~~ acne, warts) Conversion into SCC and other types of skin cancer
Missing information	Treatment of immunosuppressed patients Safety in patients with skin type I (Fitzpatrick) Safety in pediatric or adolescent patients

*requested within EMEA/H/C/002204/R/0023 but updated RMP submitted with this variation

Pharmacovigilance plan

Table 48: Ongoing and planned studies in the PhV development plan

Study/activity Type, title and category (1-3)*	**Objectives**	**Safety concerns addressed**	**Status**	**Date of submission of final study report**
Study **ALA-AK-CT009**: "A randomized, observer-blind, intra-individual phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz) in combination with daylight-PDT (photodynamic therapy) in comparison with Metvix for the treatment of mild to moderate actinic keratosis" **Category 3**	**Primary objective:** The primary objective of the study is to compare the efficacy and safety of Ameluz treatment of mild to moderate AK with Metvix when using daylight PDT. The primary efficacy variable will be the total lesion clearance rate in percent per patient's side, defined as the percentage of individual lesions with complete remission on the respective side of the patient assessed 12 weeks after PDT. **Secondary objective:** The secondary objectives of the study are to evaluate the safety and secondary efficacy parameters related to Ameluz or Metvix for the treatment of AK when using daylight PDT.	To evaluate the safety and secondary efficacy parameters related to Ameluz or Metvix for the treatment of AK when using daylight PDT.	Ongoing **Planned** study duration: First patient in: June 2016 (after DLP of this report) Last patient in planned: Sept 2016 Last patient out (clinical phase) planned: Dec 2016 Follow-up until: Sept 2017	Planned 2018

*Category 1 studies are imposed activities considered key to the benefit risk of the product.

Category 2 studies are specific obligations

Category 3 studie are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the updated data submitted, was of the opinion that the PV plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 49: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risk: • Application site reactions	Application site reactions are described in section 4.8 of the SmPC. Ameluz should be used under surveillance of HCPs (section 4.2 of the current and proposed SmPC).	None
Important potential risks: • Application site hypersensitivity • Transient memory impairment and Transient Global Amnesia (TGA) • Severe application site reaction in combination with photosensitizing medication or in patients with photodermatoses • Off-label use (e.g. acne, warts) • Recurrence rate in treated lesions • Conversion into SCC and other types of skin cancer	Hypersensitivity to ALA, porphyrins and excipients is listed as contraindication in section 4.3 of the SmPC. Warning against potential allergenic ingredients in section 4.4 of the SmPC. The risk of transient memory impairment during PDT is described in section 4.4 and section 4.8 of the SmPC. Photodermatoses and porphyria are listed as contra-indication in section 4.3 of the current and proposed SmPC. Risks associated with concomitant treatment with photosensitizing medication are described in section 4.4 of the SmPC. Correct indication, way of administration & posology are described in sections 4.1 and 4.2 of the SmPC (including re-assessment of treated lesions). The SmPC additionally includes differences in “Method of Administration” for the different indications. ~~Warnings concerning the non-experience regarding the use of Ameluz® in certain off-label indications is described in section 4.4 of the SmPC.~~ Identified off-label case reports as well as reports on transient memory impairment will be reported as events of special interest in post authorization PSUR. Conditions / factors that might lead to incompletely cleared lesions are described in section 4.4 of the SmPC.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Ameluz® should be used under surveillance of HCPs (section 4.2 of SmPC). Description of expected undesirable effects that also might count for off-label use is given in section 4.8 of the SmPC. Treated lesions should be re-evaluated after 3 months (section 4.2 of the SmPC)	
Important missing information: • Treatment of immuno-suppressed patients • Safety in patients with skin type I (Fitzpatrick) • Safety in pediatric or adolescent patients	Section 4.4 of the SmPC specifically advises that there is no experience within the immunosuppressed patient population None for safety in patients with skin type I. The non-existing experience with Ameluz® in paediatric or adolescent patients is indicated in section 4.2 of the current and proposed SmPC. The current and proposed package labelling und the package leaflet clearly instruct to keep the drug out of sight and reach of children. The current and proposed package leaflet clarifies that AK does not occur in children and adolescents.	None

The PRAC having considered the updated data submitted was of the opinion that the proposed routine risk minimisation measures remains sufficient to minimise the risks of the product in the proposed indications.

2.7. Update of the Product information

Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. Editorial changes have been proposed in sections 4.2, 4.4, 5.2, 6.6 and 9 of the SmPC. The Package Leaflet has been updated accordingly. There are two new warnings that have been included in section 4.4, that the use of immunosuppressants during treatment with Ameluz is not recommended and of the risk of transient global amnesia.

The Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons: The changes made to the SmPC do not lead to important changes to the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

BCC are composed of proliferating keratinocytes from basal cells of the epidermis. It generally demonstrates a relatively innocuous course, with slow growth and only minimal local extension into the dermis. BCCs are locally invasive tumours and metastases occur in less than 1 in 10,000 tumours (LeBoit, 2006). The main area of the body affected by BCC is the skin of the head or neck where 70% of primary BCC cases occur. In addition, 85% of metastatic cases and 90% of recurrent cases occur at these sites. Therefore, if treated accordingly this disease typically has a favourable prognosis.

3.1.2. Available therapies and unmet medical need

According to the National Comprehensive Cancer Network guidelines on treatments for BCC, the main objective is achieving maximal preservation of function and cosmetics. European guidelines for the management of BCC list a variety of treatment options aiming at eradicating the tumour while ensuring an acceptable cosmetic outcome for the patients[3,4,7,8] . Among therapies recommended for low risk early BCCs, these include surgical excision, radiotherapy (low wave X-ray, brachytherapy, high energy radiotherapy) and 5-fluorouracil, photodynamic therapy (PDT), particularly for the treatment of large or multiple lesions. In several European countries, methyl aminolevulinate (Metvix) with PDT has been approved for the treatment of superficial and/or nodular basal cell carcinoma unsuitable for other available therapies due to possible treatment related morbidity and poor cosmetic outcome; such as lesions on the mid-face or ears, lesions on severely sun damaged skin, large lesions, or recurrent lesions. 5-aminolevilinic acid (Ameluz), a product from the same class of products as Metvix, has been approved for the use of Actinic Keratosis. The MAH has now applied for an indication for treatment of superficial and/or nodular BCC.

3.1.3. Main clinical studies

3.2. Favourable effects

The efficacy of 5-aminolaevulinic acid in the treatment of superficial and/or nodular BCC has been demonstrated on the basis of a non-inferiority trial compared to Metvix. The inclusion criteria was for patients with lesions with thickness of <2mm (SmPC section 5.1). The primary efficacy endpoint of the study was the overall patient complete response 12 weeks after the last PDT which showed 93.4% of responders in the Ameluz group compared to 91.8% of responders in the Metvix group (97.5% one-sided CI: -6., p-value <0.0001) and an Odds ratio of 1.26 (97.5% one-sided CI). An overall complete responder was defined as a patient in whom all treated BCC lesions were completely cleared after the last PDT, i.e. after PDT-1 or after PDT-2 if re-treatment was performed. A secondary efficacy variable was the lesion complete response 12 weeks after the last PDT which showed 94.6% of responses in Ameluz group compared to 92.9% in the Metvix group. For nodular BCC, 89.3% of the lesions were cleared with Ameluz compared to 78.6% with Metvix. In addition, the relationship between patient complete response and lesion thickness at baseline as well as the relationship between lesion complete response and lesion thickness at baseline were evaluated. In the treatment of thin (≤2 mm thickness), non-aggressive (superficial and/or nodular) BCC the overall patient complete response rate 12 weeks after the last PDT was 93.4%, which is slightly higher than the comparator with 91.8% and also demonstrated non-inferiority of Ameluz compared to Metvix.

Results of other secondary and tertiary analyses, including mean percentage reduction of total lesion area 12 weeks after the last PDT, patient complete response 12 weeks after PDT-2 (PDT cycle 1), cosmetic outcome, change in skin quality assessments and patient satisfaction supported the primary analysis.

3.3. Uncertainties and limitations about favourable effects

In terms of the non-inferiority claim of Ameluz met its primary endpoint and there are no uncertainties about the favourable effects. An analysis exploring a potential relationship between patient complete response 12 weeks after the last PDT and lesion thickness at baseline indicated that baseline lesion thickness had a significant influence on patient complete response. The lesion complete response rates in both groups decreased in lesions with a baseline thickness measurement of >1.0 mm. However, as stated in section 5.1 of the SmPC, there were only a limited number of patients with number of lesions >1.0 mm. As the treatment is aimed at patients with early disease with superficial and/or nodular BCC, the lesions treated are not expected to be bigger in size than the lesions in patients that have been recruited in the clinical trial.

3.4. Unfavourable effects

All patients treated in both groups reported at least one TEAE. The most commonly reported SOC in both treatment groups was “general disorders and administration site conditions”. Frequencies were comparable between the groups. Application site pain was the most common individual TEAE in both groups, reported in 134 (97.1%) patients in the Ameluz and in 143 (100.0%) patients in the Metvix group. The most frequent skin reaction observed during PDT in both treatment groups was erythema, which was observed with slightly lower frequency in the Ameluz group compared to the Metvix group. Following the review of the safety database, the following new ADRs vision blurred (uncommon), visual impairment (uncommon), burning pain (very common), inflammation (uncommon), fatigue (uncommon) and back pain (uncommon) have been included in the section 4.8 of the SmPC.

During the post-authorisation surveillance experience, a new ADR, transient global amnesia, has been included as an important potential risk with a frequency of unknown, as it was reported in the literature. It has been included in the SmPC as a warning in section 4.4, as an ADR in 4.8 and also in the RMP as an important potential risk as there is not sufficient evidence to include it as an important identified risk. A new warning on the use of immunosuppressants was also included as patients using immunosuppressant therapy were excluded from the trial. Routine risk minimisation measure are considered sufficient to mitigate the risk as the product is administered under the supervision of a physician, a nurse or other healthcare professional experienced in the use of photodynamic therapy.

3.5. Uncertainties and limitations about unfavourable effects

There are no important uncertainties concerning the unfavourable effects (see RMP and summary of safety concerns).

3.6. Effects Table

Table 50: Effects Table for Ameluz in the treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment (data cut-off: …)

Effect	Short Description	Unit	5-aminolevulinic acid	methyl-aminolevulinic acid	Uncertainties/ Strength of evidence	References
Favourable Effects						

Effect	Short Description	Unit	5-aminolevulinic acid	methyl-aminolevulinic acid	Uncertainties/ Strength of evidence	References
Complete response of "Non-aggressive", thin (< 2 mm) basal cell carcinoma 12 weeks after last treatment		%	93.4	91.8	Data from observer blind part of the study only; FU period covering 6 and 12 months;	ALA-BCC CT 008, including 6 and 12 months FU
Local recurrence at:						
- 6 months follow up			2.9%	4.3%		
- 12 months follow up			6.7%	8.2%		
Unfavourable Effects						
severe TEAEs		%	39.1	33.6		ALA-BCC CT 008
Serious TEAEs			2.2	4.9		
Application site reactions						ALA-BCC CT 008
Application site pain		%	97.1	100		
Application site erythema		%	87.0	88.1		
Application site pruritus		%	42.8	34.3		
Application site oedema		%	30.4	36.4		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Ameluz is non-inferior to the comparator Metvix in the treatment of thin (≤2 mm thickness), superficial and/or nodular BCC, in terms of overall patient complete response rate at 12 weeks after past PDT (93.4% complete response in the PP analysis set, 2 to 4 PDT sessions in total) and overall lesion complete response rate 12 weeks after the last PDT. Clinical efficacy was re-assessed at follow-up visits 6 and 12 months after the last photodynamic therapy. Lesion recurrence rates after 6 and 12 months were 2.9% and 4.3%, respectively, for Ameluz and 6.7% and 8.2% for MAL.

Frequencies and severity of TEAEs seem to be consistent between the two treatments arms and are also consistent with the know safety profile of Ameluz in AK. There were no new important identified risks other than application site reaction which was already known. The new ADR of TGA and warning on the use of immunosuppressants are being monitored through routine PhV. Overall, the safety is considered manageable and acceptable and no additional risk minimisation activities are required.

3.7.2. Balance of benefits and risks

The CHMP is of the opinion that the benefits of Ameluz in the BCC patient population for the treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults outweigh the risks of application site reaction, erythema, pruritus, pain, and oedema. Therefore, the benefit risk balance is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

The indication for Ameluz has been aligned with the indication of Metvix, a product from the same class of PDT treatment products, as the treatment is for the same early BCC patient population. The inclusion criteria of patients in the clinical trial was limited to patients that had lesions <2 mm and excluded patient with porphyria, patients undergoing immunosuppressant therapy and patients with BCC lesions on embryonic fusion planes (i.e including portions of the scalp, ears, nose, and lips). These criteria have been reflected in the SmPC where the thickness of the lesions treated (<2 mm) is described in 5.1. There is a contraindication in 4.3 for porphyria and warnings in 4.4 that immunosuppressants should be avoided during treatment and that there is a risk to mucous membranes and eye irritation. Hence, there was no need to include these restrictions in the indication as they have been covered adequately in the SmPC.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication from "Treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2; see section 5.1) and of field cancerization" to the following:
Treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults.
Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. Editorial changes have been proposed in sections 4.2, 4.4, 5.2, 6.6 and 9 of the SmPC. The Package Leaflet and Labelling are updated accordingly. There are two new warnings that have been included in section 4.4 that the use of immunosuppressants during treatment with Ameluz is not recommended and of the risk of transient global amnesia. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.

The variation leads to amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include: Treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults. Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. Editorial changes have been proposed in sections 4.2, 4.4, 5.2, 6.6 and 9 of the SmPC. The Package Leaflet and Labelling are updated accordingly. There are two new warnings that have been included in section 4.4, that the use of immunosuppressants during treatment with Ameluz is not recommended and of the risk of transient global amnesia. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10. The RMP (version 11) is updated in accordance.

Summary

Please refer to the published Assessment Report Ameluz H-2204-II-24-AR.