Clinical trial results:
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)

Summary

EudraCT number	2013-003241-42
Trial protocol	DE GB
Global end of trial date	17 November 2015

Results information

Result version number	v1
This version publication date	01 December 2016
First version publication date	01 December 2016

Trial information

Trial identification

Sponsor protocol code	ALA-BCC-CT008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biofrontera Bioscience GmbH
Sponsor organisation address	Hemmelrather Weg 201, Leverkusen, Germany, 51377
Public contact	Clinical Trial Department, Biofrontera Bioscience GmbH, +49 2148763241, ameluz@biofrontera.com
Scientific contact	Clinical Trial Department, Biofrontera Bioscience GmbH, +49 2148763241, ameluz@biofrontera.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 November 2015
Global end of trial reached?	Yes
Global end of trial date	17 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to compare the efficacy of BF-200 ALA containing 7.8% 5-aminolevulinic acid (ALA) as active ingredient with the comparator Metvix®, containing 16% methyl-aminolevulinate in the treatment of thin, non-aggressive BCC with photodynamic therapy.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 42
Country: Number of subjects enrolled	Germany: 352
Worldwide total number of subjects	394
EEA total number of subjects	394

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	139

From 65 to 84 years	245
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Trial was conducted in Germany and Great Britain with a total of 24 sites who recruited patients. Enrollment of patients started (first patient enrolled) 28-Jan-2014.

Pre-assignment

Screening details:

Of the 394 patients enrolled in this study, 281 patients were randomized (138 patients to BF-200 ALA and 143 patients to Metvix®). 113 patients enrolled were excluded before randomization due to screening failure (104 patients), patient's decision (7 patients), and lost to FU and "other reason" (each 1 patient). All randomized patients treated.

Period 1

Period 1 title	clinical phase/ observer-blind period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Blinding implementation details:

Study medication randomized 1:1. IMPs have different consitencies. To guarantee the observer-blind status of the investigator assessing efficacy after each PDT session, a 2nd investigator/delegated person performed IMP application, daylight illumination and conducted all safety evaluations during illumination period. Randomization schedule and allocation to treatment groups were not known to the investigator&sponsor until completion of study, except in case of emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Metvix®

Arm description:

containing 16% methyl-aminolevulinate (MAL)

Arm type	Active comparator
Investigational medicinal product name	Metvix®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

The dose for Metvix® was up to 1 g per PDT session (depending on size and number of target lesions located on neck, trunk, extremities, face or scalp, no more than 2 illumination areas with a maximum area including margin of 10 cm^2, and a film thickness of about 1 mm). Up to 4 administrations of study treatment, which included PDT sessions (PDT-1, PDT-2, PDT-3, and PDT-4) were applied. For all patients, PDT-1 was to be administered directly after randomization and PDT-2 was to be administered approximately 1 week later. The total number of PDT sessions per patient depended on response as follows: Complete responders (lesions totally cleared clinically) 12 weeks after PDT-2: entered the FU part of the study with no further treatment. Partial or non-responders 12 weeks after PDT-2 were retreated with the same study treatment by applying 2 additional PDTs in a second PDT cycle and then entered FU.

Arm title	BF-200 ALA

Arm description:

BF-200 ALA (also referred to as Ameluz®) containing 7.8% 5-aminolevulinic acid (5-ALA)

Arm type	Experimental

Investigational medicinal product name	BF-200 ALA
Investigational medicinal product code	
Other name	Ameluz
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

The dose for BF-200 ALA was up to 1 g per PDT session (depending on size and number of target lesions located on neck, trunk, extremities, face or scalp, no more than 2 illumination areas with a maximum area including margin of 10 cm^2, and a film thickness of about 1 mm). Up to 4 administrations of study treatment, which included PDT sessions (PDT-1, PDT-2, PDT-3, and PDT-4) were applied. For all patients, PDT-1 was to be administered directly after randomization and PDT-2 was to be administered approximately 1 week later. The total number of PDT sessions per patient depended on response as follows: Complete responders (lesions totally cleared clinically) 12 weeks after PDT-2: entered the FU part of the study with no further treatment. Partial or non-responders 12 weeks after PDT-2 were retreated with the same study treatment by applying 2 additional PDTs in a second PDT cycle and then entered FU.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: During this study, the investigator assessing efficay after each PDT session was observer-blind. A second investigator or delegated person performed drug application, light treatment, and safety evaluation during illumination period. This was important since IMPs can be distinguised by their texture and consistency. IMPs have a comparable safety profile.

Number of subjects in period 1[2]	Metvix®	BF-200 ALA
Started	143	138
end of clinical phase/ observer-blind	132	128
Completed	132	128
Not completed	11	10
withdrawal due to AE, but in follow up phase	1	1
several reasons were merged, clinical phase	10	9

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 394 subjects enrolled. 113 not randomized, 281 randomized (143 received Metvix, 138 received BF-200-ALA). Due to non-randomized subjects, the number of enrolled subjects is not equal to the number of subjects in the clinical phase. 11 patients (Metvix)&10 patients (BF-200-ALA) did not complete the study. Note that 1 dropout per group to be accounted for an AE in follow up (due to AE recording until DBL). It was not possible to enter "10" for Metvix and "9" for BF-200-ALA for "not completed.

Baseline characteristics

Reporting groups	
Reporting group title	Metvix®
Reporting group description: containing 16% methyl-aminolevulinate (MAL)	
Reporting group title	BF-200 ALA
Reporting group description: BF-200 ALA (also referred to as Ameluz®) containing 7.8% 5-aminolevulinic acid (5-ALA)	

Reporting group values	Metvix®	BF-200 ALA	Total
Number of subjects	143	138	281
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	54	52	106
From 65-84 years	87	82	169
85 years and over	2	4	6
Age continuous Units: years			
arithmetic mean	66.3	66.6	
full range (min-max)	31 to 87	32 to 94	-
Gender categorical Units: Subjects			
Female	68	54	122
Male	75	84	159

End points

End points reporting groups	
Reporting group title	Metvix®
Reporting group description:	
containing 16% methyl-aminolevulinate (MAL)	
Reporting group title	BF-200 ALA
Reporting group description:	
BF-200 ALA (also referred to as Ameluz®) containing 7.8% 5-aminolevulinic acid (5-ALA)	

Primary: overall patient complete response assessed 12 weeks after the last PDT	
End point title	overall patient complete response assessed 12 weeks after the last PDT
End point description:	
overall patient complete response assessed 12 weeks after the last PDT. The indicated values give precentage of overall complete responders. An overall complete responder is defined as a patient in whom all treated lesions were cleared. The PP set is the primary analysis set for the analyses of the primary endpoint.	
End point type	Primary
End point timeframe:	
12 weeks after the last PDT. Please note: 2 PDT-cycles, each cycle consisting of 2 PDTs (=maximum of 4 PDTs per patient) was possible.	

End point values	Metvix®	BF-200 ALA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	121		
Units: percent				
arithmetic mean (confidence interval 95%)	91.8 (84.6 to 96)	93.4 (87 to 96.9)		

Statistical analyses

Statistical analysis title	Difference in % points to BF-200 ALA
Comparison groups	Metvix® v BF-200 ALA
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Farrington and Manning (non-inferiority)
Parameter estimate	Mean difference (final values)
Point estimate	1.6

Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-6.5

Secondary: Lesion complete response assessed 12 weeks after the last PDT

End point title	Lesion complete response assessed 12 weeks after the last PDT

End point description:

Lesion complete response (completely cleared individual lesions) assessed 12 weeks after the last PDT. The indicated values give precentage of overall completly cleared individual lesions. The PP set is the primary analysis set for the analyses of the secondary endpoint.

End point type	Secondary

End point timeframe:

12 weeks after the last PDT.
Please note: 2 PDT-cycles, each cycle consisting of 2 PDTs (=maximum of 4 PDTs per patient) was possible.

End point values	Metvix®	BF-200 ALA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110[1]	121[2]		
Units: percent				
arithmetic mean (confidence interval 95%)	92.9 (86.6 to 96.5)	94.6 (89.3 to 97.5)		

Notes:

[1] - this is the number of patients that received Metvix. They had 127 lesions in total.

[2] - This is the number of patients that received BF-200 ALA. They had 148 lesions in total.

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction of total lesion area 12 weeks after last PDT compared to baseline

End point title	Reduction of total lesion area 12 weeks after last PDT compared to baseline

End point description:

Reduction of total lesion area (summation of sizes of all treated lesions) per patient, assessed 12 weeks after the last PDT. The PP set is the primary analysis set for the analyses of the secondary endpoint.

Please note that the high SD for BF-200 ALA is due to a patient who had increased lesion area from 63 square-mm at baseline to 225 square-mm 12 weeks after PDT. This lesion area included a lesion that was later confirmed to be benign skin condition (lentigo solaris).

End point type	Secondary

End point timeframe:

12 weeks after the last PDT.
Please note: 2 PDT-cycles, each cycle consisting of 2 PDTs (=maximum of 4 PDTs per patient) was possible.

End point values	Metvix®	BF-200 ALA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	121		
Units: percent				
arithmetic mean (standard deviation)	-97 (± 13.37)	-94.5 (± 35.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cosmetic outcome 12 weeks after last PDT (sum score at baseline of 0 to 3)

End point title	Cosmetic outcome 12 weeks after last PDT (sum score at baseline of 0 to 3)

End point description:

The PP set is the primary analysis set for the analyses of the secondary endpoint.

End point type	Secondary

End point timeframe:

12 weeks after the last PDT.
Please note: 2 PDT-cycles, each cycle consisting of 2 PDTs (=maximum of 4 PDTs per patient) was possible.

End point values	Metvix®	BF-200 ALA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	120		
Units: percent				
arithmetic mean (confidence interval 95%)				
very good	14.7 (8.9 to 23)	23.3 (16.3 to 32.1)		
good	18.3 (11.8 to 27.2)	11.7 (6.8 to 19.1)		
satisfactory	29.4 (21.2 to 39)	35.8 (27.4 to 45.2)		
unsatisfactory	20.2 (13.3 to 29.2)	14.2 (8.7 to 22)		
impaired	17.4 (11.1 to 26.1)	15 (9.4 to 22.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cosmetic oucome 12 weeks after last PDT (sum score at baseline of 1 to 3, 0 excluded)

End point title	Cosmetic oucome 12 weeks after last PDT (sum score at baseline of 1 to 3, 0 excluded)

End point description:

End point type	Secondary

End point timeframe:

12 weeks after the last PDT.
Please note: 2 PDT-cycles, each cycle consisting of 2 PDTs (=maximum of 4 PDTs per patient) was possible.

End point values	Metvix®	BF-200 ALA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	70		
Units: percent				
arithmetic mean (confidence interval 95%)				
very good	21.6 (13.2 to 33)	40 (28.7 to 52.4)		
good	27 (17.7 to 38.8)	20 (11.7 to 31.6)		
satisfactory	32.4 (22.3 to 44.4)	22.9 (14 to 34.7)		
unsatisfactory	12.2 (6.1 to 22.3)	11.4 (5.4 to 21.8)		
impaired	6.8 (2.5 to 15.7)	5.7 (1.8 to 14.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient complete response, 12 weeks after PDT-2

End point title	Patient complete response, 12 weeks after PDT-2

End point description:

End point type	Secondary

End point timeframe:

12 weeks after PDT-2.
Please note, 2 PDT-cycles, each consisting of 2 PDTs (=maximum of PDTs per patient) was possible.

End point values	Metvix®	BF-200 ALA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	121		
Units: percent				
arithmetic mean (confidence interval 95%)	56.4 (46.6 to 65.7)	57.9 (48.5 to 66.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 28-Jan-2014 (first patient's informed consent) until date of DBL (data base lock, 22-Jan-2016)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	Metvix
Reporting group description: -	
Reporting group title	BF-200 ALA
Reporting group description: -	

Serious adverse events	Metvix	BF-200 ALA	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 143 (4.90%)	3 / 138 (2.17%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 143 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 143 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	1 / 143 (0.70%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	1 / 143 (0.70%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Squamous cell carcinoma			
subjects affected / exposed	1 / 143 (0.70%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 143 (0.70%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 143 (0.70%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 143 (0.70%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 143 (0.70%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine prolapse			

subjects affected / exposed	1 / 143 (0.70%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Metvix	BF-200 ALA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	143 / 143 (100.00%)	138 / 138 (100.00%)	
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	143 / 143 (100.00%)	134 / 138 (97.10%)	
occurrences (all)	751	718	
Application site erythema			
subjects affected / exposed	126 / 143 (88.11%)	120 / 138 (86.96%)	
occurrences (all)	288	309	
Application site pruritus			
subjects affected / exposed	49 / 143 (34.27%)	59 / 138 (42.75%)	
occurrences (all)	84	91	
Application site edema			
subjects affected / exposed	52 / 143 (36.36%)	42 / 138 (30.43%)	
occurrences (all)	108	86	
Application site paresthisia			
subjects affected / exposed	39 / 143 (27.27%)	40 / 138 (28.99%)	
occurrences (all)	65	64	
Application site scab			
subjects affected / exposed	41 / 143 (28.67%)	34 / 138 (24.64%)	
occurrences (all)	49	45	
Application site induration			
subjects affected / exposed	27 / 143 (18.88%)	32 / 138 (23.19%)	
occurrences (all)	50	63	
Application site discharge			
subjects affected / exposed	24 / 143 (16.78%)	24 / 138 (17.39%)	
occurrences (all)	32	38	
Application site exfoliation			

subjects affected / exposed	12 / 143 (8.39%)	22 / 138 (15.94%)	
occurrences (all)	13	25	
Application site erosion			
subjects affected / exposed	9 / 143 (6.29%)	18 / 138 (13.04%)	
occurrences (all)	10	22	
Application site vesicles			
subjects affected / exposed	11 / 143 (7.69%)	10 / 138 (7.25%)	
occurrences (all)	13	13	
Application site discolouration			
subjects affected / exposed	8 / 143 (5.59%)	4 / 138 (2.90%)	
occurrences (all)	10	4	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	9 / 143 (6.29%)	5 / 138 (3.62%)	
occurrences (all)	11	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 143 (6.99%)	11 / 138 (7.97%)	
occurrences (all)	10	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2014	This amendment, which affected all study sites, was dated 14 November 2014, after a total of 181 patients had been enrolled and treated. Changes and clarifications to inclusion and exclusion criteria were amended to be able to enhance patient enrollment. This change was implemented to improve recruitment. Patients enrolled after this change were expected to be comparable from a medicinal point of view and no differences in efficacy and tolerability were to be expected in comparison to those patients who had already been included in the study. This assumption was based on the fact that the applied treatment is topical and locally restricted. Thus the change in the in-/exclusion criteria was not expected to influence the composition of the enrolled population.
07 May 2015	This amendment, which affected all study sites, was dated 07 May 2015 (for Protocol version 4 for Germany and the 18 May 2015 for Protocol version 4.1 in the UK), after a total of 274 or 275 patients respectively had been enrolled and treated. 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. In addition, the requirement that "all the pages of the patient information had to be initialed and dated by the patient to confirm the comprehension" was deleted because signing and dating of the last page of the ICF is sufficient according to European regulations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported