Clinical trial results:
Tolerabililty of laser-assisted cisplatin+5-fluorouracil an exploratory proof of concept study of topical combination chemotherapy for basal cell carcinoma

Summary

EudraCT number	2018-000141-39
Trial protocol	DK
Global end of trial date	07 February 2020

Results information

Result version number	v1 (current)
This version publication date	24 October 2021
First version publication date	24 October 2021

Trial information

Trial identification

Sponsor protocol code	110118

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03541252
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Dermatology, Bispebjerg Hospital
Sponsor organisation address	Nielsine Nielsens Vej 9, Copenhagen NV, Denmark, 2400
Public contact	Emily Wenande, Bispebjerg Hospital, Department of Dermatology, +45 40505590, emilycathrinew@hotmail.com
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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	08 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 February 2020
Global end of trial reached?	Yes
Global end of trial date	07 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate tolerability and efficacy of ablative fractional laser-assisted cisplatin+5-FU therapy for basal cell carcinoma

Protection of trial subjects:

Physician monitoring and care should any potential side effects arise
Topical anesthetic during laser therapies
A manually customized well (Duoderm, Denmark) demarcated the treatment area to avoid drug-induced LSRs of surrounding healthy skin.
Patients were advised to take paracetamol if they experienced pain after the procedure.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	01 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	3

From 65 to 84 years	14
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Study recruitment initiation: 17/09/2018
Recruitment completion: 11/06/2019
Single recruitment site: Department of Dermatology, Bispebjerg Hospital, Nielsine Nielsens Vej 9, 2400 Copenhagen NV, Denmark

Pre-assignment

Screening details:

Screening was performed based on inclusion criteria. Included subjects had a histologically-verified, untreated superficial or nodular BCCs on the scalp, face, extremities or trunk, >18 years of age at baseline, legally competent, Fitzpatrick skin phototype I-III, non-pregnant.
54 patients were screened for participation, 20 were included

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	AFL+cisplatin+5-FU

Arm description:

The study was an open-label uncontrolled trial. All patients received the intervention: ablative fractional laser followed by topical cisplatin and 5-fluorouracil cream

Arm type	Experimental
Investigational medicinal product name	Cisplatin 0,1%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Cutaneous use

Dosage and administration details:

60 minute topical application (0.25 ml/cm2) of 0.1% cisplatin solution

A second treatment was performed at day 30 if residual BCC persisted clinically, as evaluated by OCT or RCM.

Investigational medicinal product name	5-Fluorouracil 5%
Investigational medicinal product code	
Other name	5-FU
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

5% 5FU cream (Efudix) applied (0.125 ml/cm2) and left under occlusion. Two reapplications of 5FU are again performed by investigators on day 1 and 3–5, resulting in a total exposure period of 7 days.

A second treatment was performed at day 30 if residual BCC persisted clinically, as evaluated by OCT or RCM.

Number of subjects in period 1	AFL+cisplatin+5-FU
Started	20
Day 30	19
Month 3	19
Month 6-9	18 [1]
Month 12	17 [2]
Completed	19
Not completed	1
Consent withdrawn by subject	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 1 of the 20 patients withdrew from the study before Day 30 (thus 19 patients completed the Day 30 and Month 3 milestones)
Only patients who achieved tumor clearance at month 3 (18/19) were seen at month 6-9.
Similarly only patients who achieved tumor clearance at month 6-9 (17/18) were seen at month 12.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 1 of the 20 patients withdrew from the study before Day 30.
19 patients completed the Day 30 and Month 3 milestones.

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	3	3	
From 65-84 years	14	14	
85 years and over	3	3	
Age continuous Units: years			
arithmetic mean	75		
full range (min-max)	56 to 101	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	15	15	
Histological Subtype			
Histologically confirmed basal cell carcinoma subtype (i.e. nodular or superficial)			
Units: Subjects			
Nodular	13	13	
Superficial	7	7	
Tumor Location			
Anatomical Location			
Units: Subjects			
Face/Scalp	4	4	
Trunk/Extremities	16	16	

Subject analysis sets

Subject analysis set title	Patient population to complete the study
Subject analysis set type	Per protocol

Subject analysis set description:

Overall tumor clearance and histological subtype specific responses

Reporting group values	Patient population to complete the study		
Number of subjects	19		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	3		
From 65-84 years	14		
85 years and over	2		
Age continuous			
Units: years			
arithmetic mean	73		
full range (min-max)	56 to 89		
Gender categorical			
Units: Subjects			
Female	5		
Male	14		
Histological Subtype			
Histologically confirmed basal cell carcinoma subtype (i.e. nodular or superficial)			
Units: Subjects			
Nodular	13		
Superficial	6		
Tumor Location			
Anatomical Location			
Units: Subjects			
Face/Scalp	4		
Trunk/Extremities	15		

End points

End points reporting groups

Reporting group title	AFL+cisplatin+5-FU
Reporting group description:	
The study was an open-label uncontrolled trial. All patients received the intervention: ablative fractional laser followed by topical cisplatin and 5-fluorouracil cream	
Subject analysis set title	Patient population to complete the study
Subject analysis set type	Per protocol
Subject analysis set description:	
Overall tumor clearance and histological subtype specific responses	

Primary: Local Skin Reactions (LSRs) Baseline - Month 3

End point title	Local Skin Reactions (LSRs) Baseline - Month 3
End point description:	
Grading according to six parameters: redness, edema, flaking, crusting, pustules, and erosion. Each parameter was graded on a standardized 5point severity scale (0–4) representing none, mild, moderate, prominent, and severe. A total composite score reflecting overall LSR severity was then calculated based on the sum of all parameters (max score: 24).	
End point type	Primary
End point timeframe:	
Days 1, 3–5, 14, 30, and month 3	

End point values	AFL+cisplatin+5-FU	Patient population to complete the study		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: LSR score				
number (not applicable)	20	20		

Statistical analyses

Statistical analysis title	Fisher's exact tests
Statistical analysis description:	
Fisher's exact tests assessed differences in LSR score intensity depending on single and double treatment. P values were twosided, exact, and considered statistically significant when <0.05.	
Comparison groups	AFL+cisplatin+5-FU v Patient population to complete the study
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	≥ 0.506 [2]
Method	Fisher exact
Parameter estimate	Median difference (final values)
Point estimate	0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[1] - 1 day posttreatment, LSRs primarily consisted of erythema and edema, with a median composite score of 7/24 (IQR 6–9). Erythema peaked at days 3–5, accompanied by treatment area flaking and tumor associated erosion. As a result, composite LSR scores reached their maximum at 9 (IQR 6–11). By day 14, a thick crust had formed over eroded areas. On days 30 and month 3, a gradual decline in residual erythema was seens reflected by lower composite scores of 4 (IQR 2–6) and 2 (IQR 1–3).
[2] - No significant difference in erythema or other LSRs was detected between groups receiving single or double treatment (P ≥ 0.506).

Secondary: Histological Tumor Clearance Month 3

End point title	Histological Tumor Clearance Month 3

End point description:

BCC tumor clearance based histological evaluation (biopsy) 3 months post-treatment.

No statistical analyses have been specified for this primary end point. The study was designed as an exploratory study with no formal statistical sample size calculation. Nineteen BCCs of superficial or nodular subtype were considered sufficient to investigate benefit and risk of the treatment.

End point type	Secondary

End point timeframe:

Evaluated by biopsy at month 3

End point values	AFL+cisplatin+ 5-FU	Patient population to complete the study		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18[3]	18[4]		
Units: Whether the tumor was cleared or not				
Clear	17	17		
Residual tumor	1	1		

Notes:

[3] - Of 20 enrolled patients, one patient withdrew before this milestone and one refused biopsy

[4] - 1/19 patients refused biopsy and did this not contribute to the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Tumor Clearance Month 6

End point title	Clinical Tumor Clearance Month 6

End point description:

To monitor BCC tumor clearance based on clinical assessments and dermoscopy, supported by non-invasive imaging
No statistical analyses have been specified for this end point. The study was designed as an exploratory study with no formal statistical sample size calculation.

Taking into account all patients seen at 3 months follow-up (n=19), overall tumor remission after 6 months was 89 % (17/19) with a clearance rate of 100% (6/6) for sBCC and 85% (11/13) for nBCC (p= 1,000).

End point type	Secondary

End point timeframe:

Month 6-9

End point values	AFL+cisplatin+ 5-FU	Patient population to complete the study		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19[5]	19		
Units: Tumor clearance (Clear or no)				
Clear	17	17		
Residual	2	2		

Notes:

[5] - Patient 20 withdrew before this milestone

Statistical analyses

Statistical analysis title	Mann Whitney U

Statistical analysis description:

Nonparametric Mann-Whitney U test assessed differences in tumor response depending on BCC subtype

Comparison groups	AFL+cisplatin+5-FU v Patient population to complete the study
Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	other
P-value	= 1 [6]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[6] - No difference

Secondary: Clinical Tumor Clearance Month 12

End point title	Clinical Tumor Clearance Month 12

End point description:

To monitor BCC tumor clearance based on clinical assessments and dermoscopy, supported by non-invasive imaging
No statistical analyses have been specified for this end point. The study was designed as an exploratory study with no formal statistical sample size calculation.

Depending on subtype, clearance rates at 12 months were 100 % (6/6) for sBCC and 69 % (9/13) for nBCC (p= 0,145)

End point type	Secondary

End point timeframe:

Month 12

End point values	AFL+cisplatin+5-FU	Patient population to complete the study		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19[7]	19		
Units: Tumor clearance month 12				
Clear	15	15		
Residual	4	4		

Notes:

[7] - Patient 20 withdrew before this milestone

Statistical analyses

Statistical analysis title	Mann Whitney U
Comparison groups	AFL+cisplatin+5-FU v Patient population to complete the study
Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.145
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Secondary: Cosmesis

End point title	Cosmesis

End point description:

Cosmesis was rated by patients and physicians on 4point scale (0–3) representing “poor - 0,” “fair - 1,” “good - 2,” or “excellent - 3.”

End point type	Secondary

End point timeframe:

Month 3, Month 6-9 and Month 12

End point values	AFL+cisplatin+5-FU	Patient population to complete the study		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18[8]	18		
Units: Cosmesis Rating				
median (inter-quartile range (Q1-Q3))				
Patient-rated	2.5 (2 to 3)	2.5 (2 to 3)		
Physcian-rated	2 (2 to 3)	2 (2 to 3)		

Notes:

[8] - Cosmesis was not rated on the patient with residual at month 3

Statistical analyses

Statistical analysis title	Wilcoxon tests

Statistical analysis description:

Wilcoxon tests were used to assess differences in physician and patientreported cosmesis

Comparison groups	AFL+cisplatin+5-FU v Patient population to complete the study
Number of subjects included in analysis	36
Analysis specification	Post-hoc
Analysis type	other[9]
P-value	= 0.082
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Notes:

[9] - Physician and patientreported cosmesis was rated “good - 2” or “excellent -3” in 79% and 94% cases respectively at 3months (P = 0.082). Cosmesis was not impacted by the number of treatments patients received (P ≥ 0.212). Most patients (83%) showed persisting erythema at month 3, which in 17% was graded as “prominent.” Cosmetic outcomes were similarly rated by patients and evaluators as “good” or “excellent” in 94 % (17/18) and 100 % (17/17) of cases at 6 and 12 months (p= 0,289 and p= 0,250).

Secondary: Safety

End point title	Safety

End point description:

Safety assessment was based on the number of patients who experienced local pain/discomfort, infection, side effects to treatment. At 3month followup, any scarring or dyspigmentation was graded based on a 4point scale (0–3) (none, mild, moderate, and severe).

End point type	Secondary

End point timeframe:

Month 3, Month 6-9, Month 12

End point values	AFL+cisplatin+5-FU	Patient population to complete the study		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	19		
Units: Occurence of side effects	19	19		

Statistical analyses

Statistical analysis title	Wilcoxon tests

Statistical analysis description:

Month 3: among 18 cleared tumors, 50% presented with some degree of scarring (9/18); the severity of which was most commonly mild (67%; 6/9). Hyperpigmentation was observed in 56% (10/18), with moderate severity noted in one patient. No correlation was shown between dyspigmentation and tumor location. Mild hypopigmentation was recorded in 17% (3/18). Scarring or dyspigmentation was not impacted by number of treatments (P ≥ 0.172) or tumor subtype (P ≥ 0.186).

Comparison groups	AFL+cisplatin+5-FU v Patient population to complete the study
Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	other[10]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[10] - Mild dyspigmentation was commonly observed at 6 and 12 months. Appearance of scarring resolved in the majority of patients at 6 months (scar 8/18) and at 12 months (scar 4/17). In contrast to 3-month findings, hypopigmentation was more prominent at 6- (61%; 11/18) and at 12 months (65%; 11/17). Hyperpigmentation decreased from 56% (10/18) at 3 months to 22% (4/18) at 6 months (p= 0,267) and persisted in two patients at end of study (12% (2/17) (p= 0,065)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of inclusion to final visit at month 12

Adverse event reporting additional description:

Local skin reactions (defined per protocolas erythema, edema, crusting, flaking, pustlation, erosion) were not considered adverse events.
No systemic adverse events were deemed related to treatment timewise/based on product summaries AEs related to treatment were limited to pruritus (32%) and oozing (100%). Local pain or infection did not occur.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	6

Reporting groups

Reporting group title	AFL+cisplatin+5-FU

Reporting group description:

The study was an open-label uncontrolled trial. All patients received the intervention: ablative fractional laser followed by topical cisplatin and 5-fluorouracil cream

Serious adverse events	AFL+cisplatin+5-FU		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	AFL+cisplatin+5-FU		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)		
Cardiac disorders			
Syncope			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Palpitations			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			

Febrile infection subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2019	The protocol was amended to include two additional followup visits at month 6-9 and months 12 in order to examine long-term clearance rates of treated tumors as well as clinical side effects such as scarring, dyspigmentation, erythema and cosmesis. Thus, patients who had not presented with tumor residual at month 3 were evaluated clinically and by OCT imaging at months 6-9 as well as month 12 (provided that they remained clear at month 6-9.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Low sample size
No control group
No randomization or blinding

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32960987