Clinical trial results:
Investigations of local skin reactions and safety after combined treatment of basal cell carcinoma using ablative fractional laser and ingenol mebutate - an exloratory, prospective, open-label phase 2a trial.

Summary

EudraCT number	2017-002843-14
Trial protocol	DK
Global end of trial date	18 May 2018

Results information

Result version number	v1 (current)
This version publication date	08 March 2020
First version publication date	08 March 2020
Summary attachment (see zip file)	Abstract (Abstract.pdf)

Trial information

Trial identification

Sponsor protocol code	0407

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bispebjerg Hospital
Sponsor organisation address	Bispebjerg Bakke23, Copenhagen, Denmark, 2400
Public contact	Dermatologisk Afdeling, Bispebjerg hospital, mhaedersdal@dadlnet.dk
Scientific contact	Dermatologisk Afdeling, Bispebjerg hospital, 45 22860181, mhaedersdal@dadlnet.dk

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	31 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2018
Global end of trial reached?	Yes
Global end of trial date	18 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) to investigate local skin reactions and safety of ablative fractional laser (AFXL)-assisted ingenol mebutate treatment of basal cell carcinoma (BCC)

Protection of trial subjects:

local anaesthesia was performed in the treatment area prior to laser exposure.
A manually customized well (Duoderm!, Denmark)
demarcated the treatment area to avoid IM-induced LSRs of
surrounding healthy skin.
Patients were advised to take paracetamol if they experienced pain after the procedure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

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)	11
From 65 to 84 years	8
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark and private dermatological practices in Copenhagen, Denmark.

Pre-assignment

Screening details:

Patients were screened if they seemed to meet inclusion criteria.

Pre-assignment period milestones

Number of subjects started	20
Number of subjects completed	20

Period 1

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

Arms

Arm title	One arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ingenol mebutate
Investigational medicinal product code	
Other name	Picato
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

Immediately after Ablative Fractional Laser exposure, ingenol meditate was applied to treatment areas in a thick layer in concentrations of 0.015% to scalp and facial areas or 0.05% to nonscalp-non-facial areas. The treatment area was occluded 8 (Tegaderm!, Denmark) for two (0.05%) or 3 days (0.015%). A second treatment was performed at day 29 if residual BCC persisted clinically, as evaluated by OCT or RCM.

Number of subjects in period 1	One arm
Started	20
Completed	20

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Patients with Fitzpatrick skin type I-III were eligible for the trial if they were a minimum of 18 years old with low-risk, histologically verified superficial or nodular BCC. Low-risk tumours were defined as primary BCCs located outside of the high-risk zone,5 tumours ≤20 mm in face or scalp areas and ≤50 mm in non-face or non-scalp areas. BCCs in the high-risk zone, patients with Gorlin's syndrome and immunosuppressed patients were excluded from the study

Reporting group values	Overall trial	Total	
Number of subjects	20	20	
Age categorical			
> 18 years			
Units: Subjects			
Adults (18-64 years)	0	0	
From 65-84 years	19	19	
85 years and over	1	1	
Age continuous			
Units: years			
median	71		
inter-quartile range (Q1-Q3)	63 to 75	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	11	11	
tumor clearance			
Units: Subjects			
tumor clearance	20	20	
Basal cell carcinomas			
Units: 20			
median	20		
full range (min-max)	20 to 20	-	

Subject analysis sets

Subject analysis set title	Tumor clearance
Subject analysis set type	Full analysis

Subject analysis set description:

At day 90, overall histological clearance rate was 14 of 20 (70%; Table 2). Clearance rates were similar for superficial and nodular BCCs (P = 0.354) and for BCCs treated with 0.015% IM concentration vs. 0.05% concentration (P = 0.141). Clinical clearance rate was 13 of 20 (65%) and further six BCCs appeared clinically reduced. OCT and RCM cure rate was 12 of 20 (60%). Overall agreement between evaluation techniques was substantial (kappa = 0.796, P = 0.0001). Similarly, inter-observer agreement between evaluations of unblinded and blinded evaluators was consistent (kappa > 0.8, P < 0.0001).

Reporting group values	Tumor clearance		
Number of subjects	20		
Age categorical			
> 18 years			
Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical			
Units: Subjects			
Female	9		
Male	11		
tumor clearance			
Units: Subjects			
tumor clearance	20		
Basal cell carcinomas			
Units: 20			
median	0		
full range (min-max)	0 to 0		

End points

End points reporting groups

Reporting group title	One arm
Reporting group description: -	
Subject analysis set title	Tumor clearance
Subject analysis set type	Full analysis

Subject analysis set description:

At day 90, overall histological clearance rate was 14 of 20 (70%; Table 2). Clearance rates were similar for superficial and nodular BCCs (P = 0.354) and for BCCs treated with 0.015% IM concentration vs. 0.05% concentration (P = 0.141). Clinical clearance rate was 13 of 20 (65%) and further six BCCs appeared clinically reduced. OCT and RCM cure rate was 12 of 20 (60%). Overall agreement between evaluation techniques was substantial (kappa = 0.796, P = 0.0001). Similarly, inter-observer agreement between evaluations of unblinded and blinded evaluators was consistent (kappa > 0.8, P < 0.0001).

Primary: Tumor clearance

End point title	Tumor clearance[1]

End point description:

End point type	Primary

End point timeframe:

3 months follow up

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was designed as an exploratory study with no formal statistical sample size calculation. Twenty BCCs of superficial or nodular subtype in twenty subjects were considered sufficient to investigate benefit and risk of the treatment. Non-parametric statistics were used for LSR and cosmesis scores, and changes in blood flow measurements. Descriptive data were presented with medians and interquartile ranges (IQR). Wilcoxon matchedpairs test was used to test differences between test a

End point values	Tumor clearance			
Subject group type	Subject analysis set			
Number of subjects analysed	20[2]			
Units: 14				
Tumor clearance	14			

Notes:

[2] - Out of 20 patients, 14 BCCs cleared after treatment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were reported during the study period from patients

Adverse event reporting additional description:

AEs were mostly moderate siterelated pain and mild pruritus. Clinical scarring in terms of skin structural and pigmentation changes was observed in majority of cleared patients at day 90 [9/14 (64%)]. Cosmesis was good and scored similarly by physician and patient at day 90 (P = 0.313).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	6

Reporting groups

Reporting group title	Patients

Reporting group description: -

Serious adverse events	Patients		
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: 1 %

Non-serious adverse events	Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Patient-reported AEs were mostly moderate siterelated pain and mild pruritus. Clinical scarring in terms of skin structural and pigmentation changes was observed in majority of cleared patients at day 90 [9/14 (64%)]. Cosmesis was good and scored similarly by physician and patient at day 90 (P = 0.313).

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

Limitations of the study included the uncontrolled design, the limited sample size, different numbers of evaluated subtypes, and only 3-month follow-up. OCT assessments of BCC thickness were not included in the protocol, which may be considered

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31442334