Clinical trial results:
Biodistribution of ablative fractional laser-assisted topical delivery of Vismodegib in basal cell carcinomas.

Summary

EudraCT number	2019-002545-38
Trial protocol	DK
Global end of trial date	01 November 2022

Results information

Result version number	v1 (current)
This version publication date	16 October 2023
First version publication date	16 October 2023

Trial information

Trial identification

Sponsor protocol code	68943

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 Bakke 24, Copenhagen, Denmark, 2400
Public contact	Merete Hædersdal, Bispebjerg Hospital, Department of Dermatology, 0045 20416746, katrine.togsverd-bo@regionh.dk
Scientific contact	Merete Hædersdal, Bispebjerg Hospital, Department of Dermatology, 0045 20416746, katrine.togsverd-bo@regionh.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	01 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2022
Global end of trial reached?	Yes
Global end of trial date	01 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study aim is in BCCs exposed to AFL+topical vismodegib to determine 1) intra-tumoral vismodegib concentration and 2) the biologic response of vismodegib expressed by GLI mRNA level at 4 days. These results are compared with BCC-vismodegib concentration in patients undergoing systemic vismodegib treatment.

Protection of trial subjects:

Basal cell carcinoma as low-malignant skin cancer that occur in up to 30% of patients older than 65 years. Recruited patients will undergo no experimental curative treatment and there are therefore no risk in terms of recurrence in the study.
Patients will be secured up to 24 hours to consider their participation and can withdraw this at any time.

Background therapy:

Background therapy include conventional treatment (surgical excision, curettage and cautery, radiation therapy) for primary tumors or continous systemic vismodegib in patients already assigned to this treatment

Evidence for comparator:

No comparators are included

Actual start date of recruitment	15 August 2019
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: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	2
From 65 to 84 years	16
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients are included from Bispebjerg Hospital Department of Dermatology and Department of Oncology, Herlev Hospital

Pre-assignment

Screening details:

Histologically verified basal cell carcinoma with a size of minimum 10mmØ

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	topical vismodegib

Arm description:

Patients with simple BCC allocated topical vismodegib emulsion

Arm type	Experimental
Investigational medicinal product name	vismodegib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Cutaneous use

Dosage and administration details:

Vismodegib (Erivedge capsules) was formulated into a topical solution as a oil-in water micro-emulsion composed of phosphate buffer, tween80, soybean oil and dimethylsulfoxide. The concentration reached was 3.1-3.2mg/mL

Arm title	systemic vismodegib

Arm description:

Patients receiving systemic vismodegib (erivedge) 150 mg daily for minimum 28 days.

Arm type	Active comparator
Investigational medicinal product name	erivedge
Investigational medicinal product code	EMEA/H/C/002602
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Erivedge capsules 150 mg once daily (oral use) for minimum 28 days

Investigational medicinal product name	vismodegib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Cutaneous use

Dosage and administration details:

Vismodegib (Erivedge capsules) was formulated into a topical solution as a oil-in water micro-emulsion composed of phosphate buffer, tween80, soybean oil and dimethylsulfoxide. The concentration reached was 3.1-3.2mg/mL

Number of subjects in period 1	topical vismodegib	systemic vismodegib
Started	16	3
Completed	16	3

Baseline characteristics

Reporting groups	
Reporting group title	topical vismodegib
Reporting group description:	
Patients with simple BCC allocated topical vismodegib emulsion	
Reporting group title	systemic vismodegib
Reporting group description:	
Patients receiving systemic vismodegib (erivedge) 150 mg daily for minimum 28 days.	

Reporting group values	topical vismodegib	systemic vismodegib	Total
Number of subjects	16	3	19
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	74	79	
full range (min-max)	59 to 80	73 to 84	-
Gender categorical			
Units: Subjects			
Female	5	3	8
Male	11	0	11
BCC diameter			
Tumor area at inclusion mm2			
Units: mm			
median	154	118	
full range (min-max)	98 to 252	106 to 766	-

End points

End points reporting groups

Reporting group title	topical vismodegib
Reporting group description:	
Patients with simple BCC allocated topical vismodegib emulsion	
Reporting group title	systemic vismodegib
Reporting group description:	
Patients receiving systemic vismodegib (erivedge) 150 mg daily for minimum 28 days.	
Subject analysis set title	safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
To test safety of topical treatment	
Subject analysis set title	hedgehog pathway expression
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
To analyse changes in expression of hedgehog pathway genes	
Subject analysis set title	all patients
Subject analysis set type	Full analysis
Subject analysis set description:	
patients included with topical vismodegib treatment and systemic vismodegib treatment	

Primary: vismodegib tumor concentration

End point title	vismodegib tumor concentration
End point description:	
At treatment day, after laser treatment, the tumor was covered with a hydrocolloid well and loaded with vismodegib emulsion. The patch was covered using a permeable film to keep it contained. The remaining vismodegib emulsion was removed with the hydrocolloid bandage day 1. At day 3-4 a punch biopsy was sampled from the tumor together with a blood test to quantify tissue and plasma vismodegib concentration	
End point type	Primary
End point timeframe:	
day 3-4 after laser treatment and topical application	

End point values	topical vismodegib	systemic vismodegib	all patients	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16	3	19	
Units: micromole(s)/litre				
median (inter-quartile range (Q1-Q3))	6.2 (2.1 to 249)	9.5 (2.6 to 17.4)	6.2 (2 to 249)	

Statistical analyses

Statistical analysis title	mann-whitney
Statistical analysis description:	
comparisons were performed using mann-whitney when data were non-normally distibuted	

Comparison groups	topical vismodegib v systemic vismodegib
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: vismodegib plasma concentration

End point title	vismodegib plasma concentration

End point description:

End point type	Secondary

End point timeframe:

vismodegib plasma concentration day 3-4 after topical application laser and vismodegib emulsion

End point values	topical vismodegib	systemic vismodegib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	3		
Units: micromole(s)/litre				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	8.9 (8.8 to 13.7)		

Statistical analyses

Statistical analysis title	mann-whitney
Comparison groups	topical vismodegib v systemic vismodegib
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: gli1

End point title	gli1

End point description:

End point type	Secondary

End point timeframe:

day 3 versus baseline

End point values	topical vismodegib	systemic vismodegib	hedgehog pathway expression	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16	3	16	
Units: percentage	51	0	51	

Statistical analyses

Statistical analysis title	change gli1 expression
Comparison groups	topical vismodegib v hedgehog pathway expression
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	t-test, 2-sided

Secondary: gli2 reduction

End point title	gli2 reduction

End point description:

End point type	Secondary

End point timeframe:

day 3-4 versus baseline values

End point values	topical vismodegib	systemic vismodegib	hedgehog pathway expression	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16	3	16	
Units: percent				
median (inter-quartile range (Q1-Q3))	55 (18 to 93)	0 (0 to 0)	55 (18 to 93)	

Statistical analyses

Statistical analysis title	mann-whitney
Comparison groups	topical vismodegib v hedgehog pathway expression

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	change gli2 expression
Comparison groups	topical vismodegib v hedgehog pathway expression
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	t-test, 2-sided

Secondary: ptch 1 reduction	
End point title	ptch 1 reduction
End point description:	

End point type	Secondary
End point timeframe:	
day 3-4 versus baseline	

End point values	topical vismodegib	systemic vismodegib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	3		
Units: percent				
median (inter-quartile range (Q1-Q3))	73 (17 to 92)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	change ptch 1 expression
Comparison groups	topical vismodegib v systemic vismodegib
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: ptch 2 reduction

End point title	ptch 2 reduction

End point description:

End point type	Secondary

End point timeframe:

day 3-4 versus baseline

End point values	topical vismodegib	systemic vismodegib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	3		
Units: percent				
median (inter-quartile range (Q1-Q3))	73 (6 to 85)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	change ptch 2 expression
Comparison groups	systemic vismodegib v topical vismodegib
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: local skin reactions

End point title	local skin reactions[1]

End point description:

End point type	Secondary

End point timeframe:

day 3 after lasre and topical vismodegib

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This was a descriptive assessment - as the other arm did not receive treatment there is nothing to be tested against

End point values	topical vismodegib	safety		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	16	16		
Units: event				
skin reaction	1	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: overall study	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	1
Reporting groups	
Reporting group title	Topical vismodegib arm

Reporting group description: -

Serious adverse events	Topical vismodegib arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (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	Topical vismodegib arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)		
Infections and infestations			
localized skin infection	Additional description: skin infection in laser-treated skin		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

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

None reported