Clinical trial results:
A randomised double blind, placebo controlled study of the efficacy of topical menthol for pain relief during topical photodynamic therapy.

Summary

EudraCT number	2015-002849-59
Trial protocol	GB
Global end of trial date	13 November 2019

Results information

Result version number	v1 (current)
This version publication date	17 December 2020
First version publication date	17 December 2020

Trial information

Trial identification

Sponsor protocol code	2015PQ01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Dundee
Sponsor organisation address	Ninewells Hospital, Dundee, United Kingdom, DD1 9SY
Public contact	Professor Sally Ibbotson, University of Dundee, 1382383297 01382383297, s.h.ibbotson@dundee.ac.uk
Scientific contact	Professor Sally Ibbotson, University of Dundee, 1382383297 01382383297, s.h.ibbotson@dundee.ac.uk

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	06 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2019
Global end of trial reached?	Yes
Global end of trial date	13 November 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Is the pain of topical photodynamic therapy (PDT) significantly different when using menthol in aqueous cream applied before PDT compared with PDT using only placebo (aqueous cream).

Protection of trial subjects:

The objective of the study was to assess potential pain relief during standard PDT treatment. Potential participants received a participant information sheet, which detailed the requirements of the study before they attended clinic for screening. All participants had >24h to read the Participant information sheet and to discuss the study with family, friends, staff involved in the study. Written informed consent was obtained prior to any study specific procedures,

Background therapy:

The background therapy was ALA photodynamic therapy used as standard routine practice for actinic keratoses of the face and scalp according to licensed practice.

Evidence for comparator:

Cell and animal model data derived during our own pre-clinical studies indicated that menthol was likely to be effective for pain relief during PDT alone. The rationale for including the placebo was that we could not be sure that menthol would be effective for pain relief when used in humans. Wright et al., Pain. 2018 Feb;159(2):284-297. doi: 10.1097/j.pain.0000000000001096.

Actual start date of recruitment	29 January 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	United Kingdom: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	0
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients referred to the photodynamic therapy clinic at Ninewells Hospital, UK with actinic keratoses on both sides of the face and scalp. First patient recruited 23.10.18 and last patient recruited 12.6.19

Pre-assignment

Screening details:

Patients >18 years with actinic keratoses on both sides of face and scalp and able to provide informed consent. 40 patients screened and 10 recruited. Patients not recruited declined because of extra time needed for study (4), requested alternative AK treatment (8), not meeting study criteria (5), unknown reasons (3).

Pre-assignment period milestones

Number of subjects started	10
Number of subjects completed	10

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Assessors (Dermatologist, technologist, nurse, data analyst) were not aware of which side received which intervention. It is possible that patients (from sensation [cooling] of menthol) might not remain fully blinded. Patients were instructed not to tell those assessors if they suspected they knew which intervention was applied to each side. After treatment, patients were asked to provide an opinion as to which treatment was applied to each side. Menthol vapour in the room helped with blinding

Arms

Are arms mutually exclusive?	No
Arm title	5% menthol in aqueous cream

Arm description:

5% menthol in aqueous cream (active IMP) applied to one half of face/scalp

Arm type	Active comparator
Investigational medicinal product name	5% menthol in aqueous cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

5% W/W MENTHOL IN AQUEOUS CREAM applied to active site

Arm title	AQUEOUS CREAM

Arm description:

Aqueous cream applied to other half of face/scalp

Arm type	Placebo

Investigational medicinal product name	aqueous cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

aqueous cream applied to placebo treated area

Number of subjects in period 1	5% menthol in aqueous cream	AQUEOUS CREAM
Started	10	10
Completed	10	10

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description:

10 patients recruited for this paired within subject comparison study and completed study - so 20 units of randomisation as 2 sites compared against each other within each suject

Reporting group values	overall trial	Total	
Number of subjects	10	10	
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)	0	0	
From 65-84 years	10	10	
85 years and over	0	0	
Age continuous Units: years			
median	80		
full range (min-max)	69 to 84	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	9	9	

Subject analysis sets

Subject analysis set title	Pain of PDT - menthol treated side
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All 10 subjects with analysis of the within-subject comparison of the primary endpoint of pain immediately after PDT, comparing sides of face/scalp exposed to IMP or placebo - reporting on menthol exposed side

Subject analysis set title	Pain of PDT - placebo treated side
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo treated side reported on

Reporting group values	Pain of PDT - menthol treated side	Pain of PDT - placebo treated side	
Number of subjects	10	10	
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)	0	0	
From 65-84 years	10	10	
85 years and over	0	0	
Age continuous			
Units: years			
median			
full range (min-max)			
Gender categorical			
Units: Subjects			
Female	1	1	
Male	9	9	

End points

End points reporting groups

Reporting group title	5% menthol in aqueous cream
Reporting group description:	
5% menthol in aqueous cream (active IMP) applied to one half of face/scalp	
Reporting group title	AQUEOUS CREAM
Reporting group description:	
Aqueous cream applied to other half of face/scalp	
Subject analysis set title	Pain of PDT - menthol treated side
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All 10 subjects with analysis of the within-subject comparison of the primary endpoint of pain immediately after PDT, comparing sides of face/scalp exposed to IMP or placebo - reporting on menthol exposed side	
Subject analysis set title	Pain of PDT - placebo treated side
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Placebo treated side reported on	

Primary: Pain immediately after PDT comparing IMP and placebo treated sides within subject

End point title	Pain immediately after PDT comparing IMP and placebo treated sides within subject
End point description:	
Pain measured by VAS 0-10cm scale immediately after PDT comparing IMP and placebo treated sides	
End point type	Primary
End point timeframe:	
Pain immediately after PDT	

End point values	5% menthol in aqueous cream	AQUEOUS CREAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: VAS 0-10cm				
arithmetic mean (full range (min-max))	6.58 (2 to 10)	6.31 (2 to 10)		

Statistical analyses

Statistical analysis title	paired T-test comparing IMP and placebo
Statistical analysis description:	
Paired T-test and associated methods to calculate confidence interval to compare VAS pain scores between IMP and placebo treated sides immediately after PDT	
Comparison groups	AQUEOUS CREAM v 5% menthol in aqueous cream

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [1]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.82
Variability estimate	Standard deviation
Dispersion value	0.77

Notes:

[1] - two-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During IMP and placebo application	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	2.1
Reporting groups	
Reporting group title	All participants
Reporting group description:	
Adverse events that may have related to IMP/placebo were documented. Other than minor headache in two patients, no other adverse events were observed. The inflammatory phototoxic insult of PDT is expected and was due to the expected effect of PDT itself.	

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)		
Nervous system disorders			
headache	Additional description: mild headache in two patients, one reported over 6 days and one reported over 7 days. unlikely related to IMP/placebo.		
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2019	protocol amended dated 27th March 2019 version 6 - in order to include interim analysis of data in light of new information available regarding alternative less painful PDT treatments available for the condition under study. The approval dates for the interim analysis (AM03) are: 29/5/19 (REC) and 8/7/19 (MHRA)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 September 2019	protocol amended dated 27th March 2019 version 6 - in order to include interim analysis of data in light of new information available regarding alternative less painful PDT treatments available for the condition under study - leading to interruption and premature discontinuation of study Dr Dawe, study statistician undertook interim analysis and recommended not continuing the study based on interim analysis, dated 6/9/19.	-

Notes:

Limitations and caveats

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

Early termination of study meant small number of recruits and data for analysis. However, during the time of the study an alternative less painful daylight PDT became routinely and widely available

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29194091