Clinical trial results:
Topical Ingenol mebutate versus 5% 5-fluorouracil versus 5% Imiquimod versus photodynamic therapy in the treatment of actinic keratosis: a multi-center randomized efficacy and cost-effectiveness study

Summary

EudraCT number	2014-003691-23
Trial protocol	NL
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021
Summary attachment (see zip file)	Results of the primary outcome in article (NEJMoa1811850.pdf)

Trial information

Trial identification

Sponsor protocol code	50621

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02281682
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Academisch ziekenhuis Maastricht (AzM)
Sponsor organisation address	P. Debyelaan 25 , Maastricht, Netherlands, 6229 HX
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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	Interim
Date of interim/final analysis	19 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Primary outcome measure: treatment success (i.e. the proportion of patients with ≥75% lesion reduction in the number of AK lesions counted at baseline in the treatment area) 12 months post treatment.

Objective long-term follow-up: Proportion of patients who develop a squamous cell carcinoma in the treatment area during study follow-up (12 months), and long-term follow-up.

Protection of trial subjects:

The rights and well-being of human subjects are protected

Background therapy: -

Evidence for comparator:

PDT involves the application of 5-aminolevulinic acid (5-ALA) or methyl aminolevulinate (MAL) to the affected skin (by means of a cream), which is converted within the cells into the photosensitizer protoporphyrin IX. Surface illumination with 585-720 nm is then used to trigger the photodynamic reaction causing destruction of tumour cells by both apoptosis and necrosis. MAL-PDT (Metvix®, Galderma) has been registered for treatment of AK in Europe.
Imiquimod (registered for treatment of AK)is based on an immunomodulating mechanism which enhances the production of cytokines and natural killer cells, the proliferation of B cells and the activation of Langerhans cells, thereby stimulating the immune response. This treatment causes inflammation due to stimulation of the immune response at the tumour site resulting in erythema, oedema, scaling and erosions.
5-FU cream (registered for treatment of AK) is a topically applied chemical ablative agent that inhibits DNA synthesis, prevents cell proliferation, and causes tumour necrosis. Similar side-effects as mentioned with Imiquimod occur during treatment with 5-FU.
IM gel is a novel topical product, which is approved by Medicines Evaluation Board (MEB) and reimbursed by the Dutch healthcare insurances (as well as the other products) by health care insurances since October 2013. IM is a pleotropic effector inducing cell death and activates the immune response.

Actual start date of recruitment	01 January 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
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	Netherlands: 624
Worldwide total number of subjects	624
EEA total number of subjects	624

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)	83
From 65 to 84 years	511
85 years and over	30

Subject disposition

Recruitment

Recruitment details:

patients who visit the outpatient departments of one of the participating centres because of AK, can be recruited. The eligible patients will be informed about the study by their treating resident in dermatology or dermatologist. If the patient is interested he/she will receive detailed patient information, including the informed consent form.

Pre-assignment

Screening details:

From November 2014 through March 2017, a total of 1174 patients were assessed for eligibility.

Pre-assignment period milestones

Number of subjects started	624
Number of subjects completed	

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	5-fluourouracil

Arm description:

5% 5-fluourouracil cream twice daily for 4 weeks

Arm type	Active comparator
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	Efudix
Pharmaceutical forms	Cream
Routes of administration	Topical

Dosage and administration details:

5% 5-Fluorouracil cream (Efudix®, Meda Pharma B.V., Amstelveen, the Netherlands) was self-applied twice daily for 4 weeks. Each patient received one tube of 40 grams independent of the treatment area size.

Arm title	imiquimod

Arm description:

5% imiquimod cream,

Arm type	Active comparator
Investigational medicinal product name	imiquimod
Investigational medicinal product code	
Other name	Aldara
Pharmaceutical forms	Cream
Routes of administration	Topical

Dosage and administration details:

The 5% imiquimod cream (Aldara®, Meda Pharma B.V., Solna, Sweden) was self-applied once daily, 3 days a week (Monday-Wednesday-Friday), for 4 consecutive weeks. Per area of 25 cm2 one sachet of 250 mg was used per day.

Arm title	MAL-PDT

Arm description:

methyl aminolevulinate photodynamic therapy (MAL-PDT), 1 session

Arm type	Active comparator
Investigational medicinal product name	methyl aminolevulinate cream
Investigational medicinal product code	
Other name	MAL cream
Pharmaceutical forms	Cream
Routes of administration	Topical

Dosage and administration details:

PDT treatment was performed by trained nurses who applied a thin (1 mm) layer of MAL cream (Metvix®, Galderma SA, Penn Pharmaceutical Services, Gwent, UK) to the treatment area, followed by coverage with light blocking aluminum foil and occlusive dressing (Tegaderm®, 3M, Leiden, the Netherlands) for 3 hours. Consecutively, the area was illuminated with a light emitting diode (LED): Aktilite® (Galderma, SA, Lausanne, Switzerland) or Omnilux® (Waldmann phototherapeutics, London, UK) with an optimum wavelength of 635 ± 18 nm (fluence 37 J/cm2 during 7.23 minutes). Directly after illumination the treatment area was covered up for 24 hours. Per 25 cm2 of treatment area, 2 grams of MAL cream were used.

Arm title	ingenol mebutate

Arm description:

0.015% ingenol mebutate gel.

Arm type	Active comparator
Investigational medicinal product name	Ingenol mebuate
Investigational medicinal product code	
Other name	Picato
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

Ingenol mebutate 0.015% gel (Picato®, LEO Pharma A/S, Bellerup, Denmark) was applied by the patient
once daily for 3 consecutive days. Per 25 cm2 of treatment area, one tube (0.47 gram) per day was used.

Notes:

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

Justification: The investigator was blinded. Patients could not be blinded due to the ivestigated treatment options

Number of subjects in period 1	5-fluourouracil	imiquimod	MAL-PDT
Started	155	156	156
Completed	155	156	156

Number of subjects in period 1	ingenol mebutate
Started	157
Completed	157

Baseline characteristics

Reporting groups	
Reporting group title	5-fluourouracil
Reporting group description:	
5% 5-fluourouracil cream twice daily for 4 weeks	
Reporting group title	imiquimod
Reporting group description:	
5% imiquimod cream,	
Reporting group title	MAL-PDT
Reporting group description:	
methyl aminolevulinate photodynamic therapy (MAL-PDT), 1 session	
Reporting group title	ingenol mebutate
Reporting group description:	
0.015% ingenol mebutate gel.	

Reporting group values	5-fluourouracil	imiquimod	MAL-PDT
Number of subjects	155	156	156
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) From 65-84 years 85 years and over			
Age continuous			
73 (48–94)			
Units: years median full range (min-max)	 74 48 to 90	 73 59 to 89	 73 55 to 90
Gender categorical Units: Subjects			
Female Male	19 136	13 143	16 140

Reporting group values	ingenol mebutate	Total	
Number of subjects	157	624	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)		0 0 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			
73 (48–94)			
Units: years			
median	72		
full range (min-max)	51 to 94	-	
Gender categorical			
Units: Subjects			
Female	18	66	
Male	139	558	

End points

End points reporting groups

Reporting group title	5-fluourouracil
Reporting group description:	
5% 5-fluourouracil cream twice daily for 4 weeks	
Reporting group title	imiquimod
Reporting group description:	
5% imiquimod cream,	
Reporting group title	MAL-PDT
Reporting group description:	
methyl aminolevulinate photodynamic therapy (MAL-PDT), 1 session	
Reporting group title	ingenol mebutate
Reporting group description:	
0.015% ingenol mebutate gel.	

Primary: Primary end-point: treatment success

End point title	Primary end-point: treatment success
End point description:	
Primary outcome measure is adequate treatment success, defined as the proportion of participants at 12 months post final treatment, with ≥ 75% reduction in the number of AK lesions counted at baseline in the treatment area (≥ 75% patient clearance at 12 m Status: Not ready for collecting values	
End point type	Primary
End point timeframe:	
3 and 12 months after end of treatment	

End point values	5-fluourouracil	imiquimod	MAL-PDT	ingenol mebutate
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	155	156	156	157
Units: AK	75	54	38	29

Statistical analyses

Statistical analysis title	Intention to treat primary outcome
Statistical analysis description:	
The primary outcome measure (treatment success) will be described as percentages (number of patients with ≥75% lesion reduction from baseline (n) / number of patients randomized (N)). Other data will be described as mean (+/- standard deviation, range), median as appropriate. The primary outcome (i.e., the proportion of patients with ≥75% lesion reduction within 12 months) will be compared between the treatment groups using an intention-to-treat analysis.	
Comparison groups	5-fluourouracil v imiquimod v MAL-PDT v ingenol mebutate

Number of subjects included in analysis	624
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
12 months	
Adverse event reporting additional description:	
Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational treatment. All adverse events reported spontaneously by the subject or observed by the investiga¬tor or his staff will be recorded.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	CCMO
Dictionary version	Art. 1 lid

Reporting groups	
Reporting group title	5-fluourouracil
Reporting group description:	
5% 5-fluourouracil cream twice daily for 4 weeks	
Reporting group title	imiquimod
Reporting group description:	
5% imiquimod cream,	
Reporting group title	MAL-PDT
Reporting group description:	
methyl aminolevulinate photodynamic therapy (MAL-PDT), 1 session	
Reporting group title	ingenol mebutate
Reporting group description:	
0.015% ingenol mebutate gel.	

Serious adverse events	5-fluourouracil	imiquimod	MAL-PDT
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 151 (0.00%)	0 / 153 (0.00%)	0 / 155 (0.00%)
number of deaths (all causes)	2	1	1
number of deaths resulting from adverse events	0	0	0

Serious adverse events	ingenol mebutate		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 151 (0.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	5-fluourouracil	imiquimod	MAL-PDT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 151 (82.78%)	103 / 153 (67.32%)	113 / 155 (72.90%)
Skin and subcutaneous tissue disorders			
skin reaction due to treatment	Additional description: Patient reported adverse events such as erythema, swelling, erosion, crusting, appearing of vesicles/bullae, scaling and itching were obtained through the diary, using a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe).		
subjects affected / exposed	125 / 151 (82.78%)	103 / 153 (67.32%)	113 / 155 (72.90%)
occurrences (all)	1	1	1

Non-serious adverse events	ingenol mebutate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 151 (88.74%)		
Skin and subcutaneous tissue disorders			
skin reaction due to treatment	Additional description: Patient reported adverse events such as erythema, swelling, erosion, crusting, appearing of vesicles/bullae, scaling and itching were obtained through the diary, using a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe).		
subjects affected / exposed	134 / 151 (88.74%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2019	Extra long-term follow-up visit to assess the number of squamous cell carcinoma during 12 months after treatment and long-term (up to five years after treatment).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30855743