Clinical trial results:
Primary Imiquimod Treatment versus Surgery for Vulvar Intraepithelial Neoplasia:
A Prospective Randomized Controlled Trial

Summary

EudraCT number	2012-002052-17
Trial protocol	AT
Global end of trial date	11 February 2021

Results information

Result version number	v1 (current)
This version publication date	02 June 2022
First version publication date	02 June 2022

Trial information

Trial identification

Sponsor protocol code	PITVIN

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medizinische Universität Graz
Sponsor organisation address	Auenbruggerplatz 14, Graz, Austria, 8036
Public contact	Univ.- Frauenklinik Graz, Medizinische Universität Graz, 43 316385 12150, kks@medunigraz.at
Scientific contact	Univ.- Frauenklinik Graz, Medizinische Universität Graz, 43 316385 12150, kks@medunigraz.at

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	04 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The present study aims to compare primary imiquimod treatment with the standard treatment (surgery) for treatment of VIN (complete clinical response).

Protection of trial subjects:

Trial subjects will be invited for a clinical follow-up (medical history and clinical examination)
Subjects will be identified with Study IDs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, 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	Austria: 110
Worldwide total number of subjects	110
EEA total number of subjects	110

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)	88
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

146 patients assessed for eligibility
36 excluded (16 did not meet inclusion criteria, 20 declined to participüate)
110 enrolled and randomly assigned

Pre-assignment

Screening details:

Patients with histologically confirmed vulvar HSIL

Period 1

Period 1 title	Study enrollment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Imiquimod

Arm description:

Topical treatment with Imiquimod

Arm type	Experimental
Investigational medicinal product name	Imiquimod
Investigational medicinal product code	
Other name	Aldara
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

Treatment with imiquimod was self-administered for a period of 4 months with possible extension to 6 months. Patients were handed a package of 5% imiquimod cream (Aldara®, Mylan) and received comprehensive oral and written instructions for usage. They were instructed to apply a thin layer of cream on the affected area remaining overnight without a cover in a slowly escalating dosage scheme: once a week for two weeks, twice a week the following two weeks, and if tolerated, 3 times a week for the last weeks

Arm title	Surgery

Arm description:

Patients allocated to surgical treatment were informed about the surgical procedure at the study center, and written informed consent was obtained. The type of surgery, i.e. excision or ablation, was based on clinical findings and the surgeon`s judgement and was performed according to the standard procedures of the clinical trial site.

Arm type	Surgery

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Imiquimod	Surgery
Started	56	54
Completed	54	53
Not completed	2	1
Consent withdrawn by subject	-	1
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Imiquimod
Reporting group description:	
Topical treatment with Imiquimod	
Reporting group title	Surgery
Reporting group description:	
Patients allocated to surgical treatment were informed about the surgical procedure at the study center, and written informed consent was obtained. The type of surgery, i.e. excision or ablation, was based on clinical findings and the surgeon`s judgement and was performed according to the standard procedures of the clinical trial site.	

Reporting group values	Imiquimod	Surgery	Total
Number of subjects	56	54	110
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	54.0	49.0	
inter-quartile range (Q1-Q3)	44.0 to 67.0	43.0 to 60.0	-
Gender categorical			
only female patients were included			
Units: Subjects			
Female	56	54	110
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Intention-to-treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT analysis was performed in 107 patients (54 imiquimod, 53 surgery)	
Subject analysis set title	Per-protocoll population
Subject analysis set type	Per protocol
Subject analysis set description:	
98 patients completed the study per-protocol (46 imiquimod and 52 surgery)	

Reporting group values	Intention-to-treat population	Per-protocoll population	
Number of subjects	107	98	
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 Units: years			
median	51.0	51.5	
inter-quartile range (Q1-Q3)	43.0 to 62.0	44.0 to 62.0	
Gender categorical			
only female patients were included			
Units: Subjects			
Female	107		
Male	0		

End points

End points reporting groups

Reporting group title	Imiquimod
Reporting group description:	
Topical treatment with Imiquimod	
Reporting group title	Surgery
Reporting group description:	
Patients allocated to surgical treatment were informed about the surgical procedure at the study center, and written informed consent was obtained. The type of surgery, i.e. excision or ablation, was based on clinical findings and the surgeon`s judgement and was performed according to the standard procedures of the clinical trial site.	
Subject analysis set title	Intention-to-treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT analysis was performed in 107 patients (54 imiquimod, 53 surgery)	
Subject analysis set title	Per-protocoll population
Subject analysis set type	Per protocol
Subject analysis set description:	
98 patients completed the study per-protocol (46 imiquimod and 52 surgery)	

Primary: Complete clinical response

End point title	Complete clinical response
End point description:	
Complete clinical response (CCR) was defined as no clinical evidence of vulvar lesion, meaning 100% reduction of primary lesion size after primary allocated study treatment (one surgical intervention or local imiquimod treatment up to 6 months). Clinical response was determined by clinical assessment and confirmed by control biopsy. In case of discrepancy between clinical evaluation and histology, the endpoint was adjusted according to the histological result.	
End point type	Primary
End point timeframe:	
The primary endpoint was clinical response at 6 months.	

End point values	Imiquimod	Surgery	Per-protocoll population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	46	52	98	
Units: Number of patients	37	41	98	

Statistical analyses

Statistical analysis title	Primary outcome
Statistical analysis description:	
To evaluate the non-inferiority of imiquimod to surgical treatment,	

the difference in CCR proportions (surgical vs imiquimod) at 6 months and the corresponding 95% CIs were estimated with the Farrington-Manning method. Imiquimod was regarded as non-inferior if the upper bound of the CI did not exceed 20%. As a sensitivity analysis of the primary endpoint, we used the Cochran-Mantel-Haenszel method to adjust the proportion difference regarding the stratum used for randomisation.

Comparison groups	Imiquimod v Surgery
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0056
Method	Farrington-Manning Test
Parameter estimate	difference in proportion
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.018
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0
Reporting groups	
Reporting group title	Imiquimod
Reporting group description: -	
Reporting group title	Surgery
Reporting group description: -	

Serious adverse events	Imiquimod	Surgery	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 56 (7.14%)	9 / 52 (17.31%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	3 / 56 (5.36%)	9 / 52 (17.31%)	
occurrences causally related to treatment / all	1 / 6	4 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy			
subjects affected / exposed	1 / 56 (1.79%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Imiquimod	Surgery	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 56 (100.00%)	52 / 52 (100.00%)	
Surgical and medical procedures			
Headache			

subjects affected / exposed	28 / 56 (50.00%)	12 / 52 (23.08%)	
occurrences (all)	28	12	
Fatigue			
subjects affected / exposed	30 / 56 (53.57%)	15 / 52 (28.85%)	
occurrences (all)	30	15	
Muscle discomfort			
subjects affected / exposed	16 / 56 (28.57%)	8 / 52 (15.38%)	
occurrences (all)	16	8	
Vulvar erosion			
subjects affected / exposed	17 / 56 (30.36%)	14 / 52 (26.92%)	
occurrences (all)	17	14	
Genital erythema			
subjects affected / exposed	30 / 56 (53.57%)	24 / 52 (46.15%)	
occurrences (all)	30	24	

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.

selection bias: only patients compliant with the study medication were included in the per-protocol analysis.
Measurement bias: patients receiving imiquimod had on average more assessments

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35483400