17 April 2020
EMA/248352/2020
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Invented name: Picato

INN: ingenol mebutate

Procedure number: EMEA/H/A-20/1489/C/002275/0030

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

Picato (ingenol mebutate) was authorised in the EU in 2012 for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults, which, left untreated, may progress to skin malignancies. However, ever since the initial marketing authorisation application evaluation, there have been concerns that Picato may induce skin tumours. In 2017, the product information of Picato was updated to reflect an excess of skin tumours (keratoacanthoma (KA)) with ingenol mebutate 0.06% compared to placebo.

Further, an imbalance in tumour incidence in the treatment area was noted in several studies for a number of skin tumour types including basal cell carcinoma (BCC), Bowen's disease and squamous cell carcinoma (SCC) between the ingenol mebutate or its related ester ingenol disoxate and comparator or placebo arms. Several explanations were proposed for these imbalances and no firm conclusions could be drawn. However, in view of the reasonable possibility that ingenol esters may be tumour-promoting in some patients, a randomised controlled trial (RCT) and a non-interventional safety study were imposed to characterise this risk and provide reassurance on safety. Concerns were then raised as to the conduct and finalisation of such RCT in a reasonable timeframe.

In view of the above concern regarding the potential risk of new skin tumour in the treatment area, and the difficulty to generate appropriate data to address the uncertainty about this risk, PRAC considered that a review of all available data including from ongoing studies and its impact on the benefit-risk balance of Picato in the authorised indication should be conducted.

On 03 September 2019 the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of Picato (ingenol mebutate) and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

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2. Scientific discussion

2.1. Introduction

The mechanism of action of ingenol mebutate for use in actinic keratosis (AK) remains to be fully characterised. In vivo and in vitro models have shown a dual mechanism of action: 1) induction of local lesion cell death and 2) promoting an inflammatory response characterised by local production of proinflammatory cytokines and chemokines and infiltration of immunocompetent cells.

Picato (ingenol mebutate) was authorised in the EU under the centralised procedure in November 2012 for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults. Picato 150 micrograms/gram gel is used on the face and scalp while Picato 500 micrograms/gram gel is used on the trunk and extremities. Left untreated AK may progress to skin malignancies.

The cumulative exposure to ingenol mebutate from MAH-sponsored clinical trials is 4,202 patients. The cumulative post-marketing patient exposure is estimated to be approximately 2.8 million treatment courses. Of note, one patient can follow a repeat treatment course on the same skin area if an incomplete response is seen at a follow-up examination after 8 weeks or other courses of treatment to treat other AK lesions.

The potential for Picato to induce skin tumours was considered during the initial marketing authorisation application evaluation. Specifically, the risk of AK progression to SCC was reflected in the

risk management plan as an important potential risk. The marketing authorisation holder (MAH) was requested to conduct a phase 4 clinical trial assessing the long-term cumulative incidence of SCC after treatment with ingenol mebutate gel, 0.015% or imiquimod cream, 5% (Aldara) for multiple AKs on face and scalp (Trial LP0041-63).

In 2017, further to data from a clinical trial (LP0105-1020) comparing ingenol mebutate 0.06% to placebo, the product information of Picato was updated to reflect an excess of a type of skin tumours (KA).

In parallel an imbalance in the incidence of SCC between the ingenol mebutate and imiquimod arms was observed in the preliminary results of the then-ongoing long-term safety study LP0041-63 imposed at time of initial marketing authorisation.

In the PSUR assessment covering the period 1 February 2018 to 31 July 2018, a requested meta-analysis of four studies of the related ester ingenol disoxate (LP0084-1193, -1194, -1195, and -1196) found a marked increase in skin tumours at 14 months in the active group compared to vehicle. An imbalance in tumour incidence was noted for a number of tumour types including BCC, Bowen's disease and SCC. However, it could not be excluded that these differences may be observer bias due to partial unblinding of investigators observing local skin responses in patients on active treatment. The pattern of tumour incidence observed in the ingenol disoxate clinical trials is not fully consistent with that observed in studies in which an imbalance in skin tumour was observed in the ingenol mebutate arm.

It was therefore difficult to draw firm conclusions from the data available in the PSUR in 2018. However, as there was a reasonable possibility that ingenol esters may be tumour-promoting in some patients, the important potential risk 'AK to SCC progression' was updated to 'New skin tumours in treatment area'. In addition, two safety studies were imposed on the marketing authorisation (European Commission (EC) decision issued on 25 April 2019) to characterise this risk and provide reassurance on long-term safety:

1. A randomised, double-blind, placebo-controlled trial in patients treated with ingenol mebutate, over at least 18 months of follow-up to further investigate the incidence of treatment area skin malignancy.

2. A cohort non-interventional post-authorisation safety study comparing patients treated with ingenol mebutate with patients exposed to other AK treatments to investigate the rate of skin malignancies.

In 2019, the scientific advice working party (SAWP) reviewed the protocol of the above mentioned imposed interventional clinical study (study 1) and considered that a substantially larger study than proposed by the MAH would be required to generate meaningful data to conclude on the risk of treatment area skin malignancy. Concerns were raised as to the conduct and finalisation of such a safety study in a reasonable timeframe.

Further, during the reporting period of the latest PSUR (1 August 2018 to 31 January 2019) an additional serious case of SCC was reported.

In view of the above concern regarding the potential risk of new skin tumours in the treatment area, and the difficulty to generate appropriate data to address the uncertainty about this risk this procedure under Article 20 of Regulation (EC) No 726/2004 was initiated to review of all available data, including from ongoing studies, and their impact on the benefit-risk balance of Picato in the authorised indication.

In the present review, the PRAC considered all data submitted by the MAH. This included data from clinical studies with ingenol mebutate, ingenol disoxate, post-marketing reports, non-clinical data and data from the literature.

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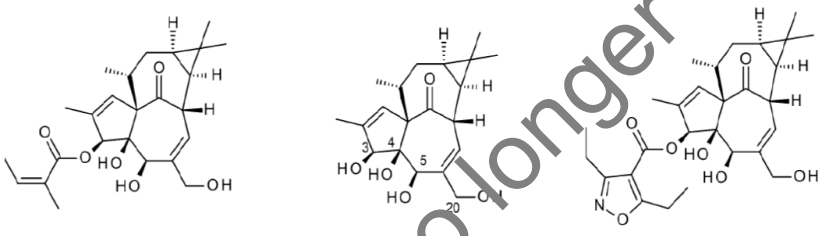
Whilst the impact of the potential risk of new skin tumours in the treatment area on the benefit-risk balance of for ingenol mebutate was not fully elucidated, based on the data available in January 2020, the PRAC considered that provisional measures were needed and recommended as a precaution that the marketing authorisations of Picato be suspended forthwith in all concerned EU Member States awaiting the adoption of the final measures (EMA/30347/2020). A Direct Healthcare Professional Communication (DHPC) was disseminated (Suspension of the marketing authorisation due to risk of skin malignancy). The European Commission (EC) issued a decision on the provisional measures on 17 January 2020. In addition, on 11 February 2020, the EC issued a decision withdrawing the marketing authorisation for Picato, at the MAH's request.

2.2. Data on safety

The MAH has provided information on all cases of skin tumours in all clinical trials with ingenol mebutate, from randomised clinical trials with ingenol disoxate and post-marketing reports of skin tumours with ingenol mebutate.

Ingenol disoxate and ingenol mebutate are related esters with a common structural element, ingenol.

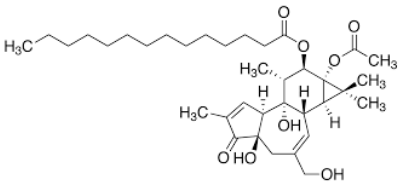
Figure 1. Comparison of the chemical structure of ingenol mebutate and ingenol disoxate



Ingenol mebutate and ingenol disoxate are considered to have a similar mechanism of action and, although presenting structural difference, to have similar biological activity. Ingenol disoxate is chemically more stable than ingenol mebutate, which potentially could lead to prolonged presence in the skin (and in particular in stratum corneum, limited by the natural turnover of keratinocytes). A 2-fold higher dermal concentration of ingenol disoxate compared to ingenol mebutate was seen in human skin 21 hours after *ex-vivo* topical application (Bertelsen, 2016). However, non-clinical data in minipigs revealed the persistence of ingenol mebutate in skin for at least 4 weeks after application (see also section 'non-clinical aspects'). Therefore, overall PRAC considered that the data currently available does not allow to conclude to a significantly different persistence in the skin between the two esters and that the ingenol disoxate safety data are relevant to ingenol mebutate.

Ingenol mebutate is structurally related to phorbol ester (12-O-tetradecanoylphorbol-13-acetate (TPA) also known as 12-myristate 13-acetate (PAM)).

Figure 2. Phorbol ester 12-o-tetradecanoylphorbol-13-acetate (TPA)



Based on the chemical structure of two esters and their analogy to phorbol ester 12-o-tetradecanoylphorbol-13-acetate which is a known tumour promoter, it cannot be excluded that they might express pro-tumourigenic properties.

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2.2.1. Data on skin tumours from clinical trials with ingenol mebutate

An overview of data on skin tumours from randomised, vehicle or active-controlled clinical trials with ingenol mebutate as AK field treatment is presented below. Data from one open-label uncontrolled study are also presented below (LP0041-62). Design allowing, statistical analyses provide pooled Mantel-Haenszel risk difference estimates, adjusted for trial.

Of note, end points definition varied across studies. One study was specifically designed to assess the long-term safety (LP0041-63). Central histopathological assessment was conducted in studies LP0105-1020, LP0105-1032 and LP0041-63. Patients were biopsied before and after treatment in two studies, LP0041-62 and -63.

2.2.1.1. 8-week follow-up, vehicle-controlled trials

Pool of ingenol mebutate in 25 cm^2 treatment areas, 8-week vehicle-controlled trials

There were 1038 subjects treated with ingenol mebutate and 790 treated with vehicle gel on a contiguous skin area of 25 cm^2 in nine studies (LP0041-03, -21, PEP005-006, -014, -015, -016, -017, -025, -028).

Skin malignancies inside the treatment area were seen in 0.1 % of the subjects treated with ingenol mebutate gel and 0.5% of those treated with vehicle gel. The corresponding figures for skin malignancies outside the treatment area were 1.6% and 2.2%, respectively. The risk difference estimates were not statistically significant: -0.5% (95% CI: -1.0%, 0.1%) in the treatment area. There were no observations of note concerning the types of skin malignancies.

Table 1. Ingenol mebutate 8-week, 25 cm^2 treatment areas, vehicle-controlled trials. Skin malignancy by trial.

	Inside treatment area						Outside treatment area					
	Ingenol mebutate			Vehicle			Ingenol mebutate			Vehicle		
Trial ID	N	E	n(%)	N	E	n(%)	N	E	n(%)	N	E	n(%)
LP0041-03	8	0	0(0.0)	8	0	0(0.0)	8	0	0(0.0)	8	0	0(0.0)
LP0041-21	158	0	0(0.0)	150	1	1(0.7)	158	5	5(3.2)	150	8	6(4.0)
PEP005-006	162	1	1(0.6)	60	1	1(1.7)	162	5	4(2.5)	60	6	3(5.0)
PEP005-014	125	0	0(0.0)	129	1	1(0.8)	125	4	2(1.6)	129	2	2(1.6)
PEP005-015	198	0	0(0.0)	66	0	0(0.0)	198	1	1(0.5)	66	0	0(0.0)
PEP005-016	132	0	0(0.0)	135	0	0(0.0)	132	1	1(0.8)	135	1	1(0.7)
PEP005-017	13	0	0(0.0)	3	0	0(0.0)	13	0	0(0.0)	3	0	0(0.0)
PEP005-025	142	0	0(0.0)	136	1	1(0.7)	142	3	2(1.4)	136	1	1(0.7)
PEP005-028	100	0	0(0.0)	103	0	0(0.0)	100	2	2(2.0)	103	6	4(3.9)
Total	1038	1	1(0.1)	790	4	4(0.5)	1038	21	17(1.6)	790	24	17(2.2)
Risk difference				-0.5%						-0.5%		
95% CI				(-1.0%,0.1%)						(-1.8%,0.9%)		

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N: Total number of subjects, E: Number of events, n: Number of subjects with at least one event.
LP0041-21: Data collected after 8 weeks (11 weeks after initial cryotherapy) not included.

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Table 2. Ingenol mebutate 8-week, 25 cm² treatment areas, vehicle-controlled trials. Skin malignancy by preferred term.

	Inside treatment area				Outside treatment area			
	Ingenol mebutate (N=1038)		Vehicle (N=790)		Ingenol mebutate (N=1038)		Vehicle (N=790)	
Preferred term	E	n(%)	E	n(%)	E	n(%)	E	n(%)
BASAL CELL CARCINOMA	0	0(0.0)	1	1(0.1)	11	9(0.9)	9	9(1.1)
BASOSQUAMOUS CARCINOMA	0	0(0.0)	1	1(0.1)	0	0(0.0)	0	0(0.0)
MALIGNANT MELANOMA	0	0(0.0)	0	0(0.0)	2	2(0.2)	2	2(0.3)
SQUAMOUS CELL CARCINOMA OF SKIN	1	1(0.1)	2	2(0.3)	8	7(0.7)	13	6(0.8)
Total	1	1(0.1)	4	4(0.5)	21	17(1.6)	24	17(2.2)

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Pool of ingenol mebutate in larger treatment areas, 8-week vehicle-controlled trials

There were 963 subjects treated with ingenol mebutate and 299 treated with vehicle gel in the pooled 8-week data from the three trials of ingenol mebutate in larger treatment areas (LP0105-1012, -1020, -1032). These show a statistically significant higher incidence of skin tumours in the ingenol mebutate groups compared to vehicle; this finding is driven by KA observed in Australian patients in the LP0105-1020 trial (risk difference in the treatment area: 1.4 (95% CI: 0.1, 2.7%)). In this study a total of 12 subjects treated with ingenol mebutate, reported 16 skin tumour events inside the treatment area (2 Bowen's disease, 3 KA, and 11 SCC). These biopsies were sent for central histopathology review where all SCCs were reclassified as KA and 1 Bowen's disease was reclassified as SCC. The original classification of the 3 KA was unchanged. No central review could be performed for one Bowen's disease tumour due to loss to follow up. Skin tumours inside the treatment area were reported a median of 33 days after start of treatment. Of the 12 subjects with skin tumours, 11 were enrolled in Australia and 1 in the US. The majority of the subjects were men, all had fair skin (Type I or Type II), and 10 subjects had a history of skin cancer, all indicative of severely sun-damaged skin and an increased risk of developing skin cancers.

Table 3. Ingenol mebutate 8-week, larger treatment area, vehicle-controlled trials. Skin tumours by trial.

	Inside treatment area						Outside treatment area					
	Ingenol mebutate			Vehicle			Ingenol mebutate			Vehicle		
Trial ID	N	E	n(%)	N	E	n(%)	N	E	n(%)	N	E	n(%)
LP0105-1012	251	0	0(0.0)	62	0	0(0.0)	251	1	1(0.4)	62	0	0(0.0)
LP0105-1020	163	12	12(7.4)	61	0	0(0.0)	163	13	10(6.1)	61	9	4(6.6)
LP0105-1032	549	6	6(1.1)	176	2	2(1.1)	549	22	18(3.3)	176	4	3(1.7)
Total	963	22	18(1.9)	299	2	2(0.7)	963	36	29(3.0)	299	13	7(2.3)
Risk difference				1.4%						0.9%		
95% CI				(0.1%,2.7%)						(-1.1%,2.9%)		

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N: Total number of subjects, E: Number of events, n: Number of subjects with at least one event.
LP0105-1032: Data from first 8 weeks only.

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Table 4. Ingenol mebutate 8-week, larger treatment areas, vehicle-controlled trials. Skin tumours by preferred term.

	Inside treatment area				Outside treatment area			
	Ingenol mebutate (N=963)		Vehicle (N=299)		Ingenol mebutate (N=963)		Vehicle (N=299)	
Preferred term	E	n(%)	E	n(%)	E	n(%)	E	n(%)
BASAL CELL CARCINOMA	1	1(0.1)	0	0(0.0)	9	9(0.9)	5	4(1.3)
BASOSQUAMOUS CARCINOMA OF SKIN	0	0(0.0)	0	0(0.0)	1	1(0.1)	0	0(0.0)
BOWEN'S DISEASE	4	4(0.4)	1	1(0.3)	9	8(0.8)	3	2(0.7)
KERATOACANTHOMA	14	10(1.0)	0	0(0.0)	1	1(0.1)	1	1(0.3)
MALIGNANT MELANOMA	0	0(0.0)	0	0(0.0)	1	1(0.1)	1	1(0.3)
MALIGNANT MELANOMA IN SITU	0	0(0.0)	0	0(0.0)	1	1(0.1)	0	0(0.0)
SQUAMOUS CELL CARCINOMA OF SKIN	3	3(0.3)	1	1(0.3)	14	13(1.3)	3	3(1.0)
Total	22	18(1.9)	2	2(0.7)	36	29(3.0)	13	7(2.3)

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2.2.1.2. 8-week follow-up, uncontrolled trial

LP0041-62, open label, uncontrolled trial

In this study ingenol mebutate gel 0.05% was used on 25 cm^2 on the arm in AK patients. Screening biopsies were performed for all participants from one of the 5-9 AKs in the selected treatment area. Biopsies identified 5 cases of Bowen's / in situ SCC and 1 invasive SCC in total 6/136 = 4.4%. These patients were excluded after screening. AK diagnosis was confirmed in 114 subjects. Finally, 108 AK patients were included and followed for 8 weeks. At study end the following skin malignancies were reported:

• inside the treatment area: 1 patient had BCC.

• outside the treatment area: 3 patients had BCC, 3 had intraepidermal carcinoma (or Bowen's disease), 4 had SCC.

2.2.1.3. Long-term follow-up, vehicle-controlled trials

LP0041-21, vehicle-controlled with 12 months of follow-up after initial cryotherapy

Skin malignancies were observed inside the treatment area in 0.6% of the subjects in the ingenol mebutate group and 2.5% of those in the vehicle group, the risk difference being non-statistically significant: –1.9% (95% CI: -4.5%, 0.8%). The Kaplan-Meier plot is displayed in the below figure.

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Table 5. LP0041-21, 12 months of follow-up after initial cryotherapy. Skin malignancy by preferred term.

	Inside treatment area				Outside treatment area[1]			
	Ingenol mebutate (N=167)		Vehicle (N=162)		Ingenol mebutate (N=167)		Vehicle (N=162)	
Preferred term	E	n(%)	E	n(%)	E	n(%)	E	n(%)
BASAL CELL CARCINOMA	1	1(0.6)	1	1(0.6)	3	3(1.8)	3	3(1.9)
MALIGNANT MELANOMA	0	0(0.0)	0	0(0.0)	1	1(0.6)	1	1(0.6)
SQUAMOUS CELL CARCINOMA	0	0(0.0)	3	3(1.9)	3	3(1.8)	4	2(1.2)
Total	1	1(0.6)	4	4(2.5)	7	7(4.2)	8	6(3.7)
Risk difference			-1.9%				0.5%	
95% CI			(-4.5%,0.8%)				(-3.7%,4.7%)	

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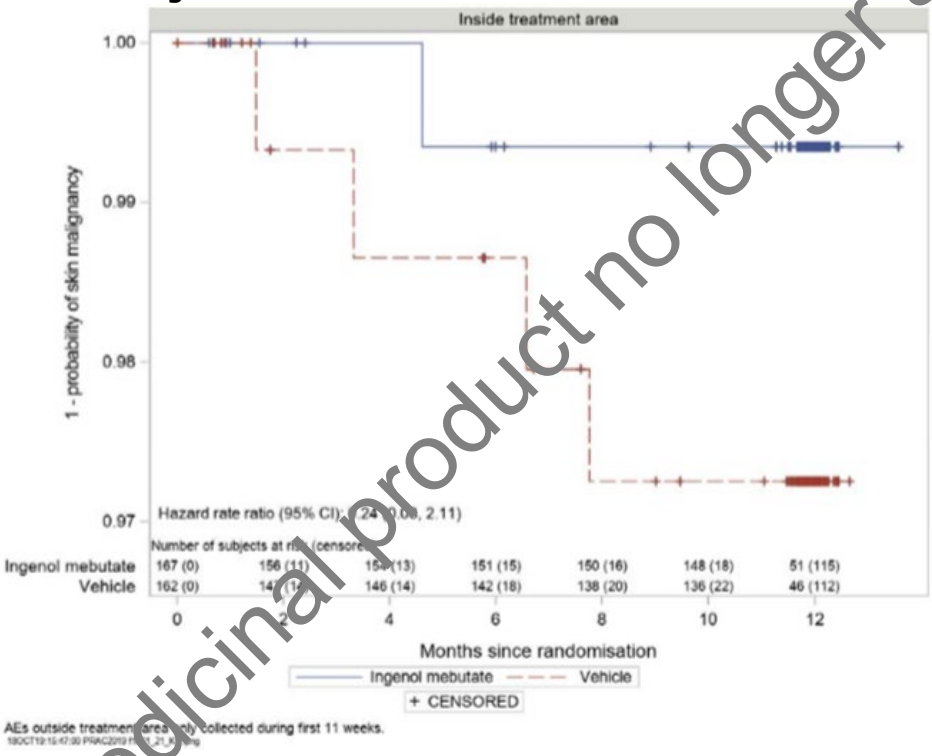
N: Total number of subjects, E: Number of events, n: Number of subjects with at least one event.
All events inside treatment area occurred after application of trial medication (Ingenol mebutate or vehicle) at Week 3.
1) AEs outside treatment area were only collected during first 11 weeks.

Figure 3. LP0041-21, 12 months of follow-up after initial cryotherapy. Kaplan-Meier curve for skin malignancies.



LP0041-22, second treatment with ingenol mebutate or vehicle, 12 months of follow-up

In this trial, all subjects received a first treatment course with ingenol mebutate, and if a second treatment course was necessary, were randomised to either ingenol mebutate or vehicle. Following the second treatment course, skin tumours were observed inside the treatment area in 0.7% of the subjects in the ingenol mebutate group and 5.8% of those in the vehicle group; the risk difference was not statistically significant: –5.1% (95% CI: –11%, 0.7%). Skin tumours outside the treatment area were balanced between the treatment groups. The Kaplan-Meier plots are displayed in the below figure.

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Table 6. LP0041-22, first treatment. Skin tumour by preferred term.

	Inside treatment area		Outside treatment area	
	Ingenol mebutate (N=450)		Ingenol mebutate (N=450)	
Preferred term	E	n(%)	E	n(%)
BASAL CELL CARCINOMA	4	3(0.7)	67	46(10)
BOWEN'S DISEASE	1	1(0.2)	10	7(1.6)
CARCINOMA IN SITU OF SKIN	0	0(0.0)	3	2(0.4)
KERATOACANTHOMA	1	1(0.2)	0	0(0.0)
SQUAMOUS CELL CARCINOMA OF SKIN	1	1(0.2)	22	19(4.2)
Total	7	6(1.3)	102	63(14)

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N: Total number of subjects, E: Number of events, n: Number of subjects with at least one event.
Follow-up from first treatment with ingenol mebutate to initiation of second treatment course or end of observation period (maximum 12 months).

Table 7. LP0041-22, second treatment. Skin tumour by preferred term.

	Inside treatment area				Outside treatment area			
	Ingenol mebutate (N=134)		Vehicle (N=69)		Ingenol mebutate (N=134)		Vehicle (N=69)	
Preferred term	E	n(%)	E	n(%)	E	n(%)	E	n(%)
BASAL CELL CARCINOMA	0	0(0.0)	0	0(0.0)	31	14(10)	15	11(16)
BASOSQUAMOUS CARCINOMA OF SKIN	1	1(0.7)	0	0(0.0)	1	1(0.7)	0	0(0.0)
BOWEN'S DISEASE	0	0(0.0)	1	1(1.4)	7	6(4.5)	3	2(2.9)
CARCINOMA IN SITU OF SKIN	0	0(0.0)	1	1(1.4)	4	1(0.7)	5	1(1.4)
KERATOACANTHOMA	0	0(0.0)	0	0(0.0)	0	0(0.0)	1	1(1.4)
MALIGNANT MELANOMA	0	0(0.0)	0	0(0.0)	1	1(0.7)	0	0(0.0)
SQUAMOUS CELL CARCINOMA OF SKIN	0	0(0.0)	3	3(4.3)	18	12(9.0)	12	6(8.7)
Total	1	1(0.7)	5	4(5.8)	62	27(20)	36	14(20)
Risk difference			-5.1%				-0.1%	
95% CI			(-11%,0.7%)				(-12%,12%)	

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N: Total number of subjects, E: Number of events, n: Number of subjects with at least one event.
Follow-up from initiation of second treatment course to end of study (12 months after first treatment).
Subject 1257 (Vehicle) non-cutaneous invasive metastatic SCC not shown in table.

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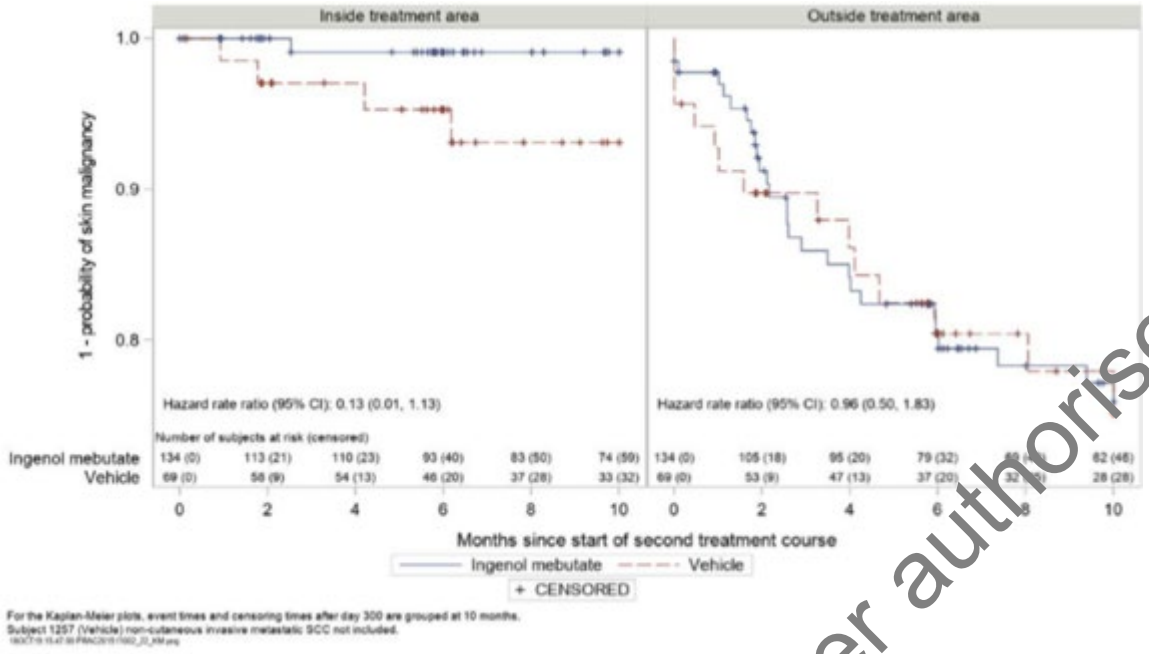
Figure 4. LP0041-22, second treatment up to 10 months follow up. Kaplan-Meier curve for skin tumours.



LP0105-1032, ingenol mebutate in larger treatment areas, 14-months of follow-up

Skin tumours were observed inside the treatment area in 7.3% of the subjects in the ingenol mebutate group and 5.1% of subjects in the vehicle group. The risk difference was not statistically significant: 2.2% (95% CI: –1.7%, 6.1%). Most of the difference is driven by BCC. The Kaplan-Meier plot shows superposed curves except for the last 2 months of follow-up.

Table 8. LP0105-1032, ingenol mebutate in larger treatment areas, 14 months of follow-up. Skin tumours by preferred term.

	Inside treatment area			
	Ingenol mebutate (N=549)		Vehicle (N=176)	
Preferred term	E	n(%)	E	n(%)
ATYPICAL FIBROXANTHOMA	1	1(0.2)	1	1(0.6)
BASAL CELL CARCINOMA	20	18(3.3)	4	4(2.3)
BOWEN'S DISEASE	14	14(2.6)	4	4(2.3)
KERATOACANTHOMA	0	0(0.0)	1	1(0.6)
MALIGNANT MELANOMA IN SITU	1	1(0.2)	0	0(0.0)
SQUAMOUS CELL CARCINOMA OF SKIN	11	9(1.6)	3	3(1.7)
Total	47	40(7.3)	13	9(5.1)
Risk difference				2.2%
95% CI				(-1.7%,6.1%)

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N: Total number of subjects, E: Number of events, n: Number of subjects with at least one event.
AEs outside the treatment area were not collected after 8 weeks.

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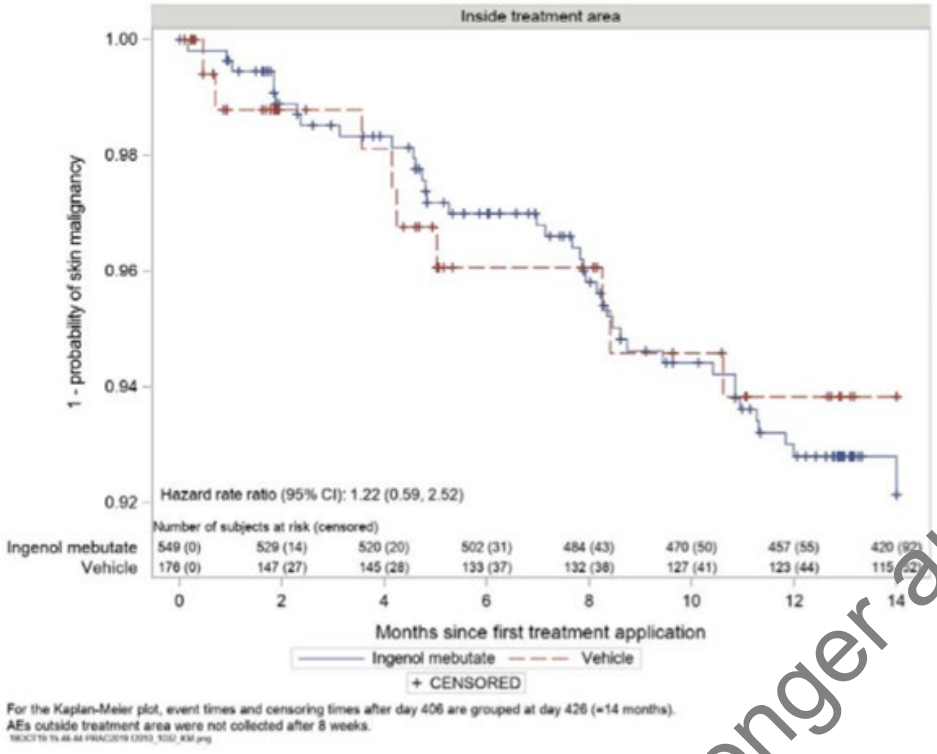
Figure 5. LP0105-1032, ingenol mebutate in larger treatment areas, 14-months of follow-up. Kaplan-Meier curve for skin tumours.



For the Kaplan-Meier plot, event times and censoring times after day 406 are grouped at day 426 (=14 months).
AEs outside treatment area were not collected after 8 weeks.

Long-term trials PEP005-030, PEP005-031, and PEP005-032

Patients who had complete clearance of AKs in the phase 3 program for Picato were followed-up for 1 year. No skin malignancies were observed in these 192 subjects.

2.2.1.4. Long-term follow-up, active-controlled trials

LP0041-63, imiquimod controlled trial with 3 years of follow-up

There were 240 subjects randomised to ingenol mebutate gel, 0.015% and 244 to imiquimod cream 5% for the treatment of AK lesions within a 25 cm² treatment area on the face or scalp. After 3 years of follow-up, skin tumours were observed inside the treatment area in 6.3% of the subjects in the ingenol mebutate group and 2.0% of those in the imiquimod group. The risk difference was statistically significant: 4.2% (95% CI: 0.7%, 7.7%). The difference was driven by SCC and Bowen's disease. Skin tumours outside the treatment area were balanced between the treatment groups.

The difference between the 2 treatment groups is developed in the period from around 3 months to 1.5 years after the first exposure. There was only one new event after 1.4 years in the ingenol mebutate group.

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Table 9. LP0041-63, 3 years follow-up. Skin tumours by preferred term.

	Inside treatment area				Outside treatment area			
	Ingenol mebutate (N=240)		Imiquimod (N=244)		Ingenol mebutate (N=240)		Imiquimod (N=244)	
Preferred term	E	n(%)	E	n(%)	E	n(%)	E	n(%)
ATYPICAL FIBROXANTHOMA	0	0(0.0)	0	0(0.0)	0	0(0.0)	1	1(0.4)
BASAL CELL CARCINOMA	4	1(0.4)	1	1(0.4)	64	36(15)	77	40(16)
BASOSQUAMOUS CARCINOMA OF SKIN	0	0(0.0)	0	0(0.0)	4	2(0.8)	0	0(0.0)
BOWEN'S DISEASE	6	6(2.5)	4	3(1.2)	11	10(4.2)	7	5(2.0)
KERATOACANTHOMA	2	1(0.4)	0	0(0.0)	1	1(0.4)	0	0(0.0)
MALIGNANT MELANOMA	0	0(0.0)	0	0(0.0)	0	0(0.0)	3	3(1.2)
SQUAMOUS CELL CARCINOMA OF SKIN	9	8(3.3)	1	1(0.4)	47	29(12)	42	27(11)
SUPERFICIAL SPREADING MELANOMA STAGE UNSPECIFIED	0	0(0.0)	0	0(0.0)	1	1(0.4)	0	0(0.0)
Total	21	15(6.3)	6	5(2.0)	128	64(27)	130	63(26)
Risk difference			4.2%				[illegible]	
95% CI			(0.7%,7.7%)				[illegible]	

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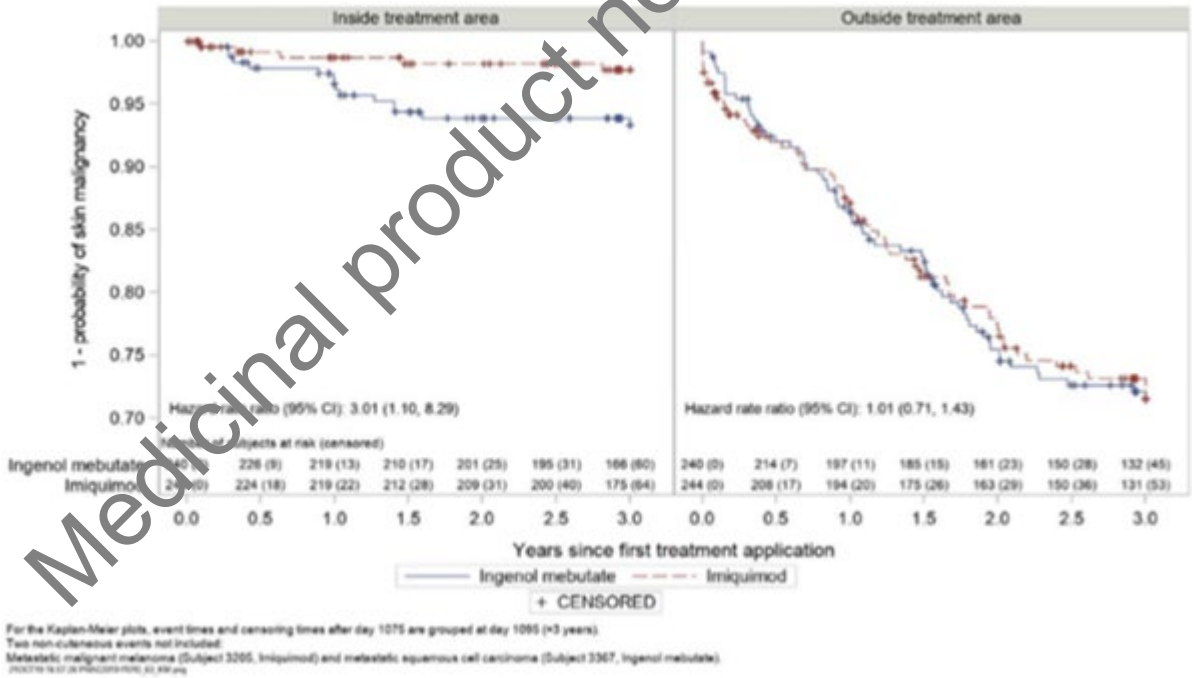
N: Total number of subjects, E: Number of events, n: Number of subjects with at least one event.
The SCC for subject 1167 (Ingenol mebutate) was included here but not included in the evaluation of the primary endpoint since the same lesion had previously been diagnosed as Bowen's disease by central evaluation.
Two non-cutaneous events not shown in table:
Metastatic malignant melanoma (Subject 3205, Imiquimod) and metastatic squamous cell carcinoma (Subject 3367, Ingenol mebutate).

Figure 6. LP0041-63, 3 years follow-up. Kaplan-Meier curve for skin tumours inside or outside treatment area.



For the Kaplan-Meier plots, event times and censoring times after day 1075 are grouped at day 1095 (=3 years).
Two non-cutaneous events not included:
Metastatic malignant melanoma (Subject 3205, Imiquimod) and metastatic squamous cell carcinoma (Subject 3367, Ingenol mebutate).

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Figure 7. LP0041-63, 3 years follow-up. Kaplan-Meier curve for skin tumours by anatomical location.

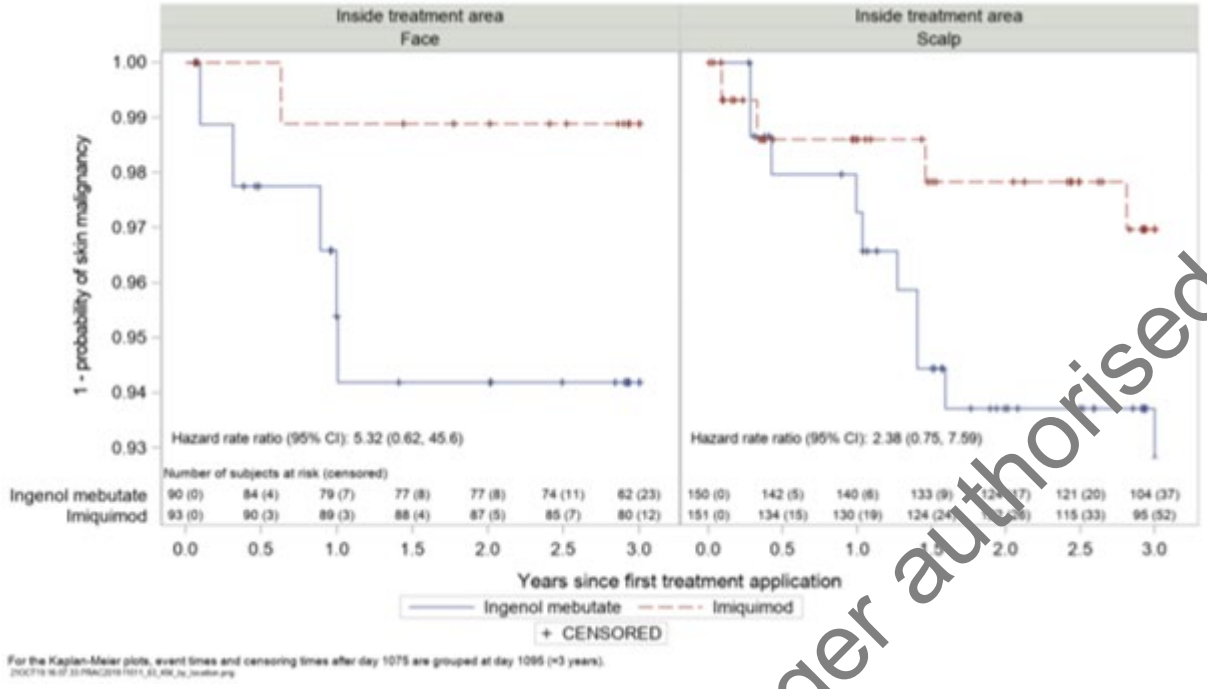

Table 10. LP0041-63, subjects with skin malignancies* inside and outside the treatment area stratified by number of actinic keratoses at baseline.

Number of AKs inside treatment area at baseline	Ingenol mebutate >= 1 SCC* Inside treatment area n/N (%)	Imiquimod >= 1 SCC* Inside treatment area n/N (%)	Ingenol mebutate >= 1 SCC* Outside treatment area n/N (%)	Imiquimod >= 1 SCC* Outside treatment area n/N (%)
0-4	0/ 0(-)	0/ 0(-)	0/ 0(-)	0/ 0(-)
5-8	11/200(5.5%)	3/200(1.5%)	29/200(14.5%)	22/200(11.0%)
>8	3/ 40(7.5%)	1/ 44(2.3%)	7/ 40(17.5%)	8/ 44(18.2%)
Total	14/240(5.8%)	4/244(1.6%)	36/240(15.0%)	30/244(12.3%)

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* Includes primary SCC, Bowen's Disease/SCC in situ, and keratoacanthoma.
n: Number of subjects with at least one SCC, within baseline AK count subcategory.
N: Total number of subjects, within baseline AK count subcategory.

In this trial with 3 years of follow-up, there is a statistically significant difference in the occurrence of skin malignancies between ingenol mebutate and the active control (imiquimod), in the treatment area. In line with epidemiological data (De Berker, 2017) the frequency of skin malignancies was higher in patients who have more than 8 AK lesions. The percentage of skin malignancies is comparable across both arms outside treatment area in this patient group (17.5% and 18.2 %), whereas it is higher in the ingenol mebutate group compared to the imiquimod group outside the treatment area in the patient group with 5-8 AK lesions at baseline (14.5% and 11.0%) and inside treatment area for both these groups (7.5% and 2.3% and 5.5 % vs. 1.5%, respectively).

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LP0041-1120, diclofenac-controlled trial with 17 weeks of follow-up

In this trial (n=481; ingenol mebutate, n=247; diclofenac, n=234), there was only 1 skin malignancy inside the treatment area, which was in the ingenol mebutate group. The risk differences were not statistically significant: 0.4 (95% CI: -0.4, 1.2%) in the treatment area.

Table 11. LP0041-1120, 17 weeks of follow-up. Skin malignancy by preferred term.

	Inside treatment area				Outside treatment area			
	Ingenol mebutate (N=247)		Diclofenac (N=234)		Ingenol mebutate (N=247)		Diclofenac (N=234)	
Preferred term	E	n(%)	E	n(%)	E	n(%)	E	n(%)
BASAL CELL CARCINOMA	0	0(0.0)	0	0(0.0)	8	7(2.8)	3	3(1.3)
BOWEN'S DISEASE	0	0(0.0)	0	0(0.0)	2	2(0.8)	2	2(0.9)
MALIGNANT MELANOMA	0	0(0.0)	0	0(0.0)	2	2(0.8)	0	0(0.0)
SQUAMOUS CELL CARCINOMA OF SKIN	1	1(0.4)	0	0(0.0)	5	4(1.6)	0	0(0.0)
Total	1	1(0.4)	0	0(0.0)	17	13(5.3)	5	5(2.1)
Risk difference			0.4%				3.1%	
95% CI			(-0.4%,1.2%)				(-0.2%,6.5%)	

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2.2.2. Data on skin tumours from clinical trials with ingenol disoxate

An overview of data on skin tumours from randomised, vehicle-controlled clinical trials with ingenol disoxate, as AK field treatment is presented below. Design allowing, statistical analyses provide pooled Mantel-Haenszel risk difference estimates, adjusted for trial.

The treatment area approved for ingenol mebutate is 25 cm^2 compared to the 250 cm^2 area investigated in the ingenol disoxate development program.

Pool of Ingenol disoxate 8-week vehicle-controlled trials

There were 1264 subjects treated with ingenol disoxate and 530 treated with vehicle gel in seven studies (LP0084-1013, -1014, -1015, -1193, -1194, -1195, -1196). Central histopathological assessment was conducted in studies LP0084-1193, -1194, -1195 and -1196.

Skin tumours inside the treatment area were seen in 0.7% of subjects treated with ingenol disoxate gel and 0.6% of those treated with vehicle gel. The corresponding figures for skin tumours outside the treatment area were 2.2% and 2.5%, respectively. The risk differences were not statistically significant: 0.2 (95% CI: -0.6%, 1.0%) in the treatment area. There were no observations of note concerning the types of skin tumours.

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Table 12. Ingenol disoxate 8-week trials. Skin tumours by trial.

	Inside treatment area						Outside treatment area					
	Ingenol disoxate			Vehicle			Ingenol disoxate			Vehicle		
Trial ID	N	E	n(%)	N	E	n(%)	N	E	n(%)	N	E	n(%)
LP0084-1013	184	0	0(0.0)	58	0	0(0.0)	184	1	1(0.5)	58	0	0(0.0)
LP0084-1014	131	0	0(0.0)	32	0	0(0.0)	131	1	1(0.8)	32	0	0(0.0)
LP0084-1015	123	2	2(1.6)	32	0	0(0.0)	123	3	1(0.8)	32	0	0(0.0)
LP0084-1193	205	3	3(1.5)	100	0	0(0.0)	205	11	11(5.4)	100	3	3(3.0)
LP0084-1194	202	4	3(1.5)	104	3	2(1.9)	202	8	7(3.5)	104	3	3(2.9)
LP0084-1195	209	1	1(0.5)	104	1	1(1.0)	209	7	5(2.4)	104	5	5(4.8)
LP0084-1196	210	0	0(0.0)	100	0	0(0.0)	210	2	2(1.0)	100	2	2(2.0)
Total	1264	10	9(0.7)	530	4	3(0.6)	1264	33	28(2.2)	530	13	13(2.5)
Risk difference				0.2%						0.1%		
95% CI				(-0.6%,1.0%)						(-1.5%,1.6%)		

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N: Total number of subjects, E: Number of events, n: Number of subjects with at least one event.
LP0084-1193,-1194,-1195 and -1196: Data from first 8 weeks only.
Mantel-Haenszel risk difference, stratified by trial.

Table 13. Ingenol disoxate 8-week trials. Skin tumours by preferred term.

	Inside treatment area				Outside treatment area			
	Ingenol disoxate (N=1264)		Vehicle (N=530)		Ingenol disoxate (N=1264)		Vehicle (N=530)	
Preferred term	E	n(%)	E	n(%)	E	n(%)	E	n(%)
ATYPICAL FIBROXANTHOMA	0	0(0.0)	0	0(0.0)	0	0(0.0)	1	1(0.2)
BASAL CELL CARCINOMA	4	4(0.3)	2	2(0.4)	14	11(0.9)	6	6(1.1)
BOWEN'S DISEASE	4	3(0.2)	2	1(0.2)	1	1(0.1)	1	1(0.2)
KERATOACANTHOMA	1	1(0.1)	0	0(0.0)	0	0(0.0)	0	0(0.0)
LENTIGO MALIGNA	0	0(0.0)	0	0(0.0)	1	1(0.1)	0	0(0.0)
MALIGNANT MELANOMA IN SITU	0	0(0.0)	0	0(0.0)	1	1(0.1)	2	2(0.4)
SQUAMOUS CELL CARCINOMA OF SKIN	1	1(0.1)	0	0(0.0)	16	16(1.3)	3	3(0.6)
Total	10	9(0.7)	4	3(0.6)	33	28(2.2)	13	13(2.5)

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Pool Ingenol disoxate, 14 months vehicle-controlled trials

Data from four 14-months randomised, vehicle-controlled trials was pooled: LP0084-1193, -1194, -1195 and -1196. The effect of the data from an observational explorative 2-year follow-up extension study of these 4 trials was also analysed (LP0084-1369 trial).

Skin tumours were observed inside the treatment area in 7.7% of subjects in the ingenol disoxate groups and 2.9% of those in the vehicle groups; the risk difference was statistically significant: 4.9% (95% CI: 2.5%, 7.3%). The difference was driven by BCC, Bowen's disease and SCC. AEs outside the treatment area were not collected after 8 weeks.

The Kaplan-Meier plots show that the curves begin to separate around month 5. Inclusion of the extra follow-up time from LP0084-1369 showed a slightly lower hazard rate ratio. The LP0084-1369 study was terminated prematurely, reportedly for commercial reasons.

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Table 14. Ingenol disoxate, 14 months follow-up. Skin tumours by trial.

	Inside treatment area					
	Ingenol disoxate			Vehicle		
Trial ID	N	E	n(%)	N	E	n(%)
LP0084-1193	205	28	22(11)	100	3	3(3.0)
LP0084-1194	202	33	26(13)	104	11	7(6.7)
LP0084-1195	209	11	11(5.3)	104	3	2(1.9)
LP0084-1196	210	5	5(2.4)	100	0	0(0.0)
Total	826	77	64(7.7)	408	17	12(2.9)
Risk difference				4.9%		
95% CI				(2.5%,7.3%)		

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Table 15. Ingenol disoxate, 14 months follow-up. Skin tumours by preferred term

	Inside treatment area			
	Ingenol disoxate (N=826)		Vehicle (N=408)	
Preferred term	E	n(%)	E	n(%)
BASAL CELL CARCINOMA	26	22(2.7)	4	4(1.0)
BOWEN'S DISEASE	27	23(2.8)	6	4(1.0)
KERATOACANTHOMA	1	1(0.1)	0	0(0.0)
MALIGNANT MELANOMA	2	2(0.2)	0	0(0.0)
SQUAMOUS CELL CARCINOMA OF SKIN	21	19(2.3)	7	5(1.2)
Total	77	64(7.7)	17	12(2.9)

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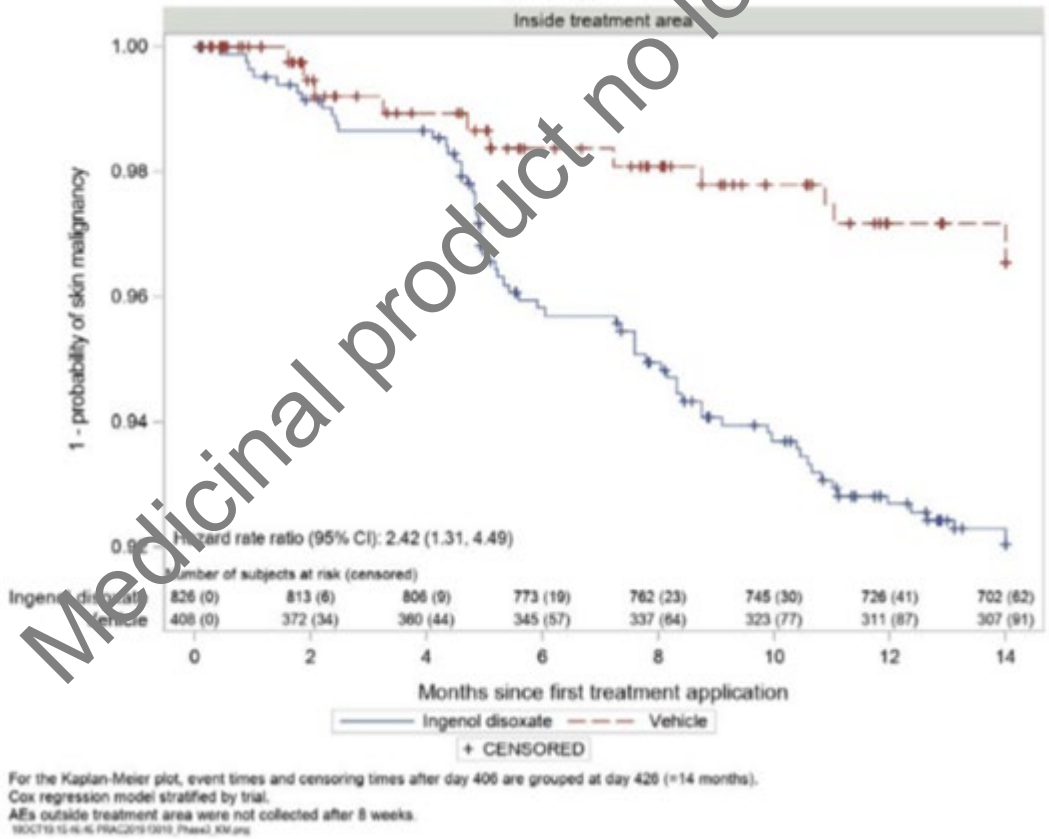
Figure 8. Ingenol disoxate, 14 months follow-up. Kaplan-Meier curve for skin tumours.



For the Kaplan-Meier plot, event times and censoring times after day 406 are grouped at day 420 (=14 months).
Cox regression model stratified by trial.
AEs outside treatment area were not collected after 8 weeks.

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Table 16. Ingenol disoxate, 14 months follow-up and additional follow-up up to 24 months from LP0084-1389. Skin tumours by preferred term.

	Inside treatment area			
	Ingenol disoxate (N=826)		Vehicle (N=408)	
Preferred term	E	n(%)	E	n(%)
BASAL CELL CARCINOMA	30	26(3.1)	4	4(1.0)
BOWEN'S DISEASE	27	23(2.8)	7	5(1.2)
KERATOACANTHOMA	1	1(0.1)	1	1(0.2)
MALIGNANT MELANOMA	3	2(0.2)	0	0(0.0)
SQUAMOUS CELL CARCINOMA OF SKIN	22	20(2.4)	8	6(1.5)
Total	83	68(8.2)	20	15(3.7)
Risk difference			4.7%	
95% CI			(2.1%, 7.2	

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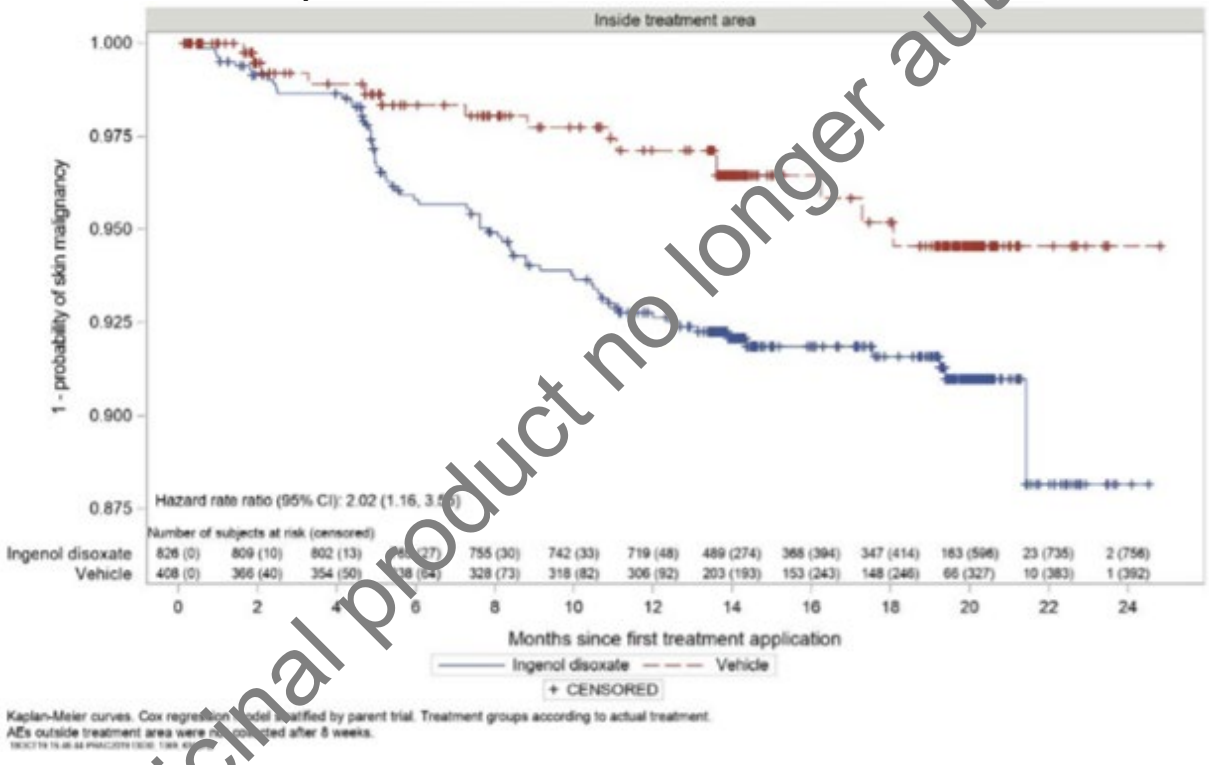
Figure 9. Ingenol disoxate, 14 months follow-up and additional follow-up up to 24 months from LP0084-1389. Kaplan-Meier curve for skin tumours.



Kaplan-Meier curves. Cox regression model stratified by parent trial. Treatment groups according to actual treatment.
AEs outside treatment area were not collected after 8 weeks.

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Figure 10. Ingenol disoxate, 14 months follow-up. Kaplan-Meier curve for skin tumours, by trial.

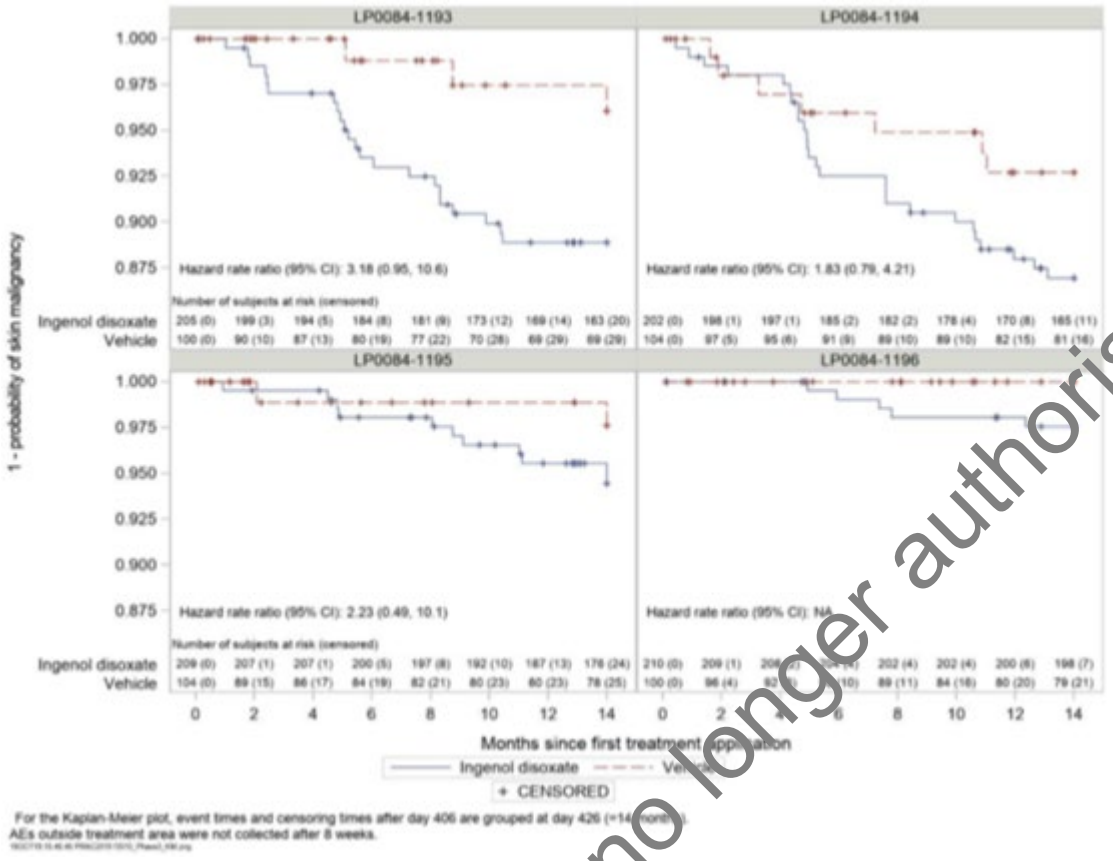
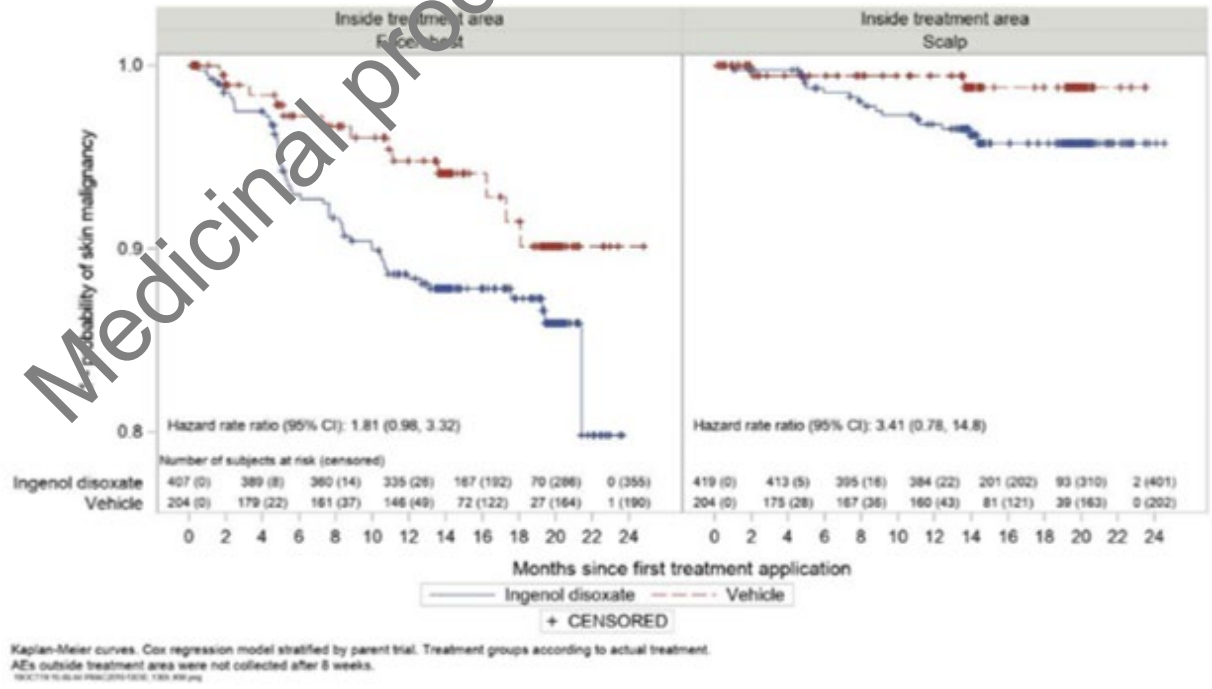


Figure 11. Ingenol disoxate, 14 months follow-up and additional follow-up up to 24 months from LP0084-1389. Kaplan-Meier curve for skin tumours by anatomical location.



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2.2.3. Pooled analyses

2.2.3.1. Skin malignancies by application site

Cox regression analyses, accounting for censorings due to withdrawals, were performed for all long-term, randomised controlled trials with ingenol mebutate or ingenol disoxate, except for the LP0084-1196 trial where no events occurred in the comparator group. Subgroup analyses by anatomical location were performed for the LP0041-63 (ingenol mebutate vs imiquimod with 3 years follow-up) and LP0084-1369 (ingenol disoxate vs vehicle with up to 24 months follow-up) trials. No violation of the proportional hazards assumption was detected in any Cox regression analyses (test for proportional hazards assumption, p-values ranging from 0.12 to 0.77).

A higher occurrence of skin tumours in the ingenol mebutate/disoxate group versus the comparator/vehicle group was observed in trials LP0105-1020 (ingenol mebutate in larger treatment areas, 8-week vehicle-controlled), LP0041-63 (ingenol mebutate vs imiquimod, 3 years follow-up), and in the vehicle-controlled ingenol disoxate phase 3 trials (LP0084-1193, 1194, 1195, 1196).

LP0105-1020: one strength of ingenol mebutate (0.06%) was studied in one anatomical location (approximately 250 cm^2 on the trunk/extremities). The 12 subjects with skin malignancies were equally distributed with 4 subjects in each of the 3 ingenol mebutate treatment groups (2-, 3-, or 4-day treatments).

LP0041-63: one strength of ingenol mebutate (0.015%) was studied. The Kaplan Meier survival curves for ingenol mebutate were very similar in the subgroups of subjects treated on the face and the scalp. The hazard rate ratio (ingenol mebutate vs. imiquimod) was numerically larger for the face than the scalp; however, the interaction between treatment and anatomical location was not statistically significant (p=0.50) when assessed in a Cox regression model with factors treatment, anatomical location (face or scalp), and interaction between treatment and anatomical location.

Ingenol disoxate phase 3 trials (including additional follow-up from trial LP0084-1369): in 2 of these trials, LP0084-1193 and LP0084-1194, subjects were treated on the face or chest with ingenol disoxate 0.018%. In the 2 other trials, i.e. LP0084-1195 and LP0084-1196, the anatomical location was the scalp and the concentration of the product was 0.037%. For both ingenol disoxate and vehicle, more events occurred in the face/chest trials compared to the scalp trials. The hazard rate ratio (ingenol disoxate vs. vehicle) was numerically larger for the combined scalp trials than the face/chest trials; however, the interaction between treatment and anatomical location was not significant (p=0.44) when assessed in a Cox regression model with factors treatment (ingenol disoxate or vehicle), anatomical location (face/chest or scalp), and interaction between treatment and anatomical location. Since the effect of dose and anatomical location cannot be separated, this also implies no evidence of a dose-response relationship. Excluding the additional data collected in the LP0084-1369 trial does not affect the conclusion.

For the remaining randomised controlled trials with ingenol mebutate/disoxate, a discussion of interaction by application site and dose-response relationship is not considered applicable since one of the following apply:

- No or very few events occurred inside the treatment area in the ingenol mebutate/disoxate group (ingenol mebutate 8-week trials, LP0041-1120, LP0105-1012, ingenol disoxate 8-week trials)

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- The occurrence of skin malignancies inside the treatment area was lower in the ingenol mebutate group compared to the vehicle group (LP0041-21, LP0041-22)
- The occurrence of skin malignancies inside the treatment area was similar in the ingenol mebutate and vehicle group and the difference was not statistically significant (LP0105-1032)

2.2.3.2. Skin malignancies before and after 4 months

The occurrence of skin malignancies, before and after 4 months, inside and outside the treatment area, for all long-term trials (i.e. duration of follow-up longer than 4 months), with ingenol mebutate and ingenol disoxate is presented cumulatively in the table below (i.e. PEP005-030, -031, -032, LP0041-21, -22, -63, LP0105-1032, LP0084-1193, -1194, 1195, -1196, -1369).

Table 17. Cumulative skin malignancies inside treatment area, before and after 4 months, based on data from long-term trials with ingenol mebutate or ingenol disoxate.

Time of analysis	**Ingenol mebutate or disoxate**			**Vehicle or active comparator**		
	Total number of subjects	Number of skin malignancies	Number of subjects with at least one skin malignancy	Total number of subjects	Number of skin malignancies	Number of subjects with at least one skin malignancy
Before 4 months	2232	34 (1.5%)	30 (1.3%)	990	11 (1.1%)	10 (1.0%)
After 4 months	2232	131 (5.9%)	111 (5.0%)	990	32 (3.2%)	25 (2.5%)

After 4 months of treatment area follow-up, there was an increase of skin malignancies in ingenol mebutate or ingenol disoxate groups compared to vehicle or other comparators groups. The inherent limitations of combining results from studies with different methodologies are noted.

2.2.3.3. Skin malignancies by disease severity and risk factors

Fitzpatrick Type Skin classifications of Type I, II, III, and IV were seen respectively in 20.9%, 59.9%, 17.6%, and 1.7% of the subjects included in study LP0041-63. As presented in the below table, the majority of skin malignancies in the LP0041-63 and LP0041-62 studies reported inside treatment area occurred in patients with Fitzpatrick skin type II.

Table 18. LP0041-63 and LP0041-62, number of skin malignancies in ingenol mebutate and imiquimod arms by skin type.

Fitzpatrick skin type	**Number and type of tumours in ingenol mebutate arm**	**Number and type of tumours in imiquimod arm**
type I	7 skin malignancies (4 BCC, 3 SCC) in 3 patients	2 skin malignancies (2 Bowen's Disease) in 1 patient
type II	12 malignancies (4 Bowen's disease, 1 BCC, 7 SCC) in 11 patients	3 malignancies (1 Bowen's disease, 1 BCC, 1 SCC) in 3 patients
type III	3 skin malignancies (2 KA, 1 Bowen's disease) in 2 patients	1 malignancy (1 Bowen's Disease) in 1 patient

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Total	**22 skin malignancies in 16 patients**	**6 skin malignancies in 5 patients**

Out of the 22 skin malignancies inside treatment area in ingenol mebutate groups, 15 occurred after 4 months.

Skin tumours inside treatment area after ingenol mebutate and imiquimod treatment from LP0041-63 trial, are respectively presented in the below tables.

Table 19. LP0041-63, skin tumours inside treatment area in ingenol mebutate arm, by skin type

Fitzpatrick skin type	Sex/Age	Number AKs inside treatment area at baseline (before/after biopsy)	Biopsy localization	History of skin cancer
type I	M/71	6/5	face	No
	M/68	6/5	face	No
	M/77	8/6	scalp	Yes, SCC and BCC
type II	M/71	7/6	scalp	No
	M/77	7/6	face	Yes, SCC
	M/71	8/7	scalp	No
	M/46	6/5	Chest (no biopsy)	Yes, BCC and Bowen's disease
	M/82	8/7	scalp	No
	M/70	9/8	face	Yes, SCC
	M/88	8/8	scalp	Yes, BCC
	M/68	7/6	face	Yes, and BCC
	M/77	7/6	scalp	Yes, SCC and BCC
	M/72	8/8	Scalp	Yes, BCC
	M/75	7/6	Scalp	Yes, SCC
type III	M/72	9 before /8 after biopsy	scalp	No
	M/73	9 before /6 after biopsy	scalp	No

Table 20. LP0041-63, skin tumours inside treatment area in imiquimod arm, by skin type

Fitzpatrick type of the skin	Sex/Age	Number AK inside treatment area	Biopsy localization	History of skin cancer
type I	M/76	7/6	scalp	No
type II	M/68	9/8	scalp	Yes, SCC
	M/91	6/5	face	Yes, SCC
	M/89	8/7	scalp	No
type III	M/65	5/4	scalp	No

In the LP004-63, all patients with skin tumour inside treatment area were men, mostly aged 70 or older in ingenol mebutate arm (mean 72.4). No patient had an immuno-compromised status (defined as cancer chemotherapy, acquired immune deficiency syndrome, organ transplantation, immunosuppressive treatment). Eleven subjects had history of skin tumour, but no information on localisation has been provided. Ten of 16 patients developed skin tumour on scalp, 5 on face and one on chest in ingenol mebutate group.

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2.2.4. Data from post-marketing reports

The MAH has provided the results of a search in its global safety database with the Standardised Medical Dictionary for Regulatory Activities Queries (MedDRA SMQ) 'Skin malignant tumours' with a data lock point on 6 September 2019. Results are presented below with a focus on aspects that could help better characterising the risk, as the relevance of this data to prove or exclude this risk is very limited.

The search identified 84 valid post-marketing reports (including solicited cases from non-interventional studies). These cases represented 91 events in the SMQ 'Skin malignant tumours'. An overview of the adverse events reported in these cases, individual details of all cases and a cumulative presentation of the reported time to onset are included in the below tables and figure.

Table 21. Overview of relevant events within SMQ "skin malignant tumours".

	No. of events with Causality: Possible (implied or reported)	No. of events with reporter causality: Not related	No. of events - Total
SCCs			
- PT 'Squamous cell carcinoma' or 'Squamous cell carcinoma of skin'	47	11	58
BCCs			
- PT 'Basal cell carcinoma'	4	2	6
- PT 'Basosquamous carcinoma'	1	0	1
- PT 'Neoplasm skin' (confirmed to be BCC)	1	0	1
Bowen's disease	3	1	4
Other			
- PT 'Keratoacanthoma'	8	0	8
- PT 'Atypical fibroxanthoma'	3	1	4
- PT 'Malignant melanoma'	3	0	3
- PT 'Lentigo maligna'	2	0	2
- PT 'Skin cancer'	2	0	2
- PT 'Neuroendocrine carcinoma of the skin'	1	0	1
- PT 'Sarcoma of skin'	1	0	1
Total	**76**	**15**	**91**

Table 22. Characteristics of post-marketing reports with the SMQ "skin malignant tumours".

Characteristic**		Number of cases
Age	≤17 years	0
	18-30 years	0
	31-50 years	1
	51-64 years	12
	65-75 years	24
	≥75 years	37
	Unknown	10
Sex	Male	52
	Female	30
	Unknown	2
Skin malignant medical history	Present	28
	Not present	13
	Not known	43
Case seriousness	Serious	71
	Non-serious	13
Location	Inside treatment area	87*
	Outside treatment area	2
	Unknown	2
Time to event onset after Picato® use	≤4 months	61
	4-8 months	8
	8-12 months	3
	≥12 months	1
	Not known	18

*23 cases reported in which the event is likely in the treatment area, however not specifically confirmed

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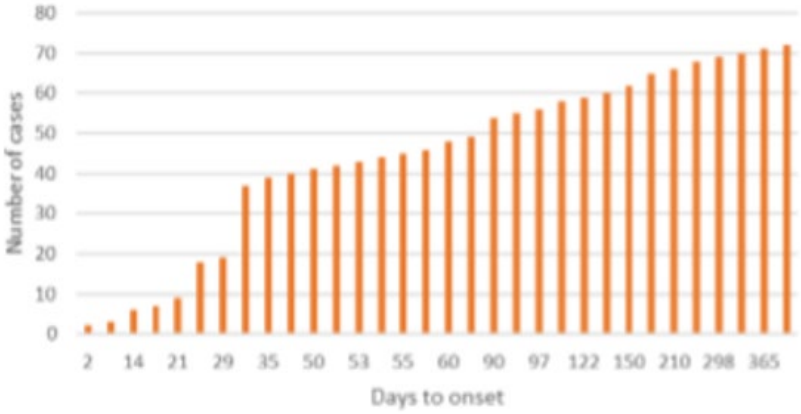
Figure 12. Time to onset cumulative reporting.



In total 58 events of SCCs, reported in 57 patients, and 4 events of Bowen´s disease, reported in 4 patients (one case reporting both Bowen's disease and SCC), originating from 60 reports were identified. Seen as a whole, the reports describe a population at high risk of developing SCC: the vast majority are of advanced age, a large number of patients have past medical history of skin malignancy and are pre-disposed as per indication of sun-damaged skin.

The majority of the reported SCC events and Bowen's disease were observed less than 4 months after ingenol mebutate treatment (43 events). In several of the cases reporting a short time to onset of 4 months or less, the identified lesions were described as fast-growing. Several of the cases report that a significant increase in size of the tumour is apparent over as little as 4 weeks or less.

Whilst most reported cases were SCC, 8 events of BCC have been reported in 8 patients. In addition, 21 events of non-melanoma skin tumours other than SCC or BCC have been reported: 8 cases of KA, 4 cases of atypical fibroxanthoma (AFX), 3 cases of malignant melanoma, 2 cases of lentigo maligna, 2 cases of unspecified skin cancer, 1 case of sarcoma of skin and 1 case of neuroendocrine carcinoma of the skin.

2.2.5. Discussion of safety data on skin tumours

In clinical trials which compare ingenol mebutate versus vehicle in 25 cm^2 treatment areas with 8-week follow-up, there is no statistically significant difference in the occurrence of skin tumours. However, when considering a larger treatment area, there is a statistically significant difference in a pooled analysis of three clinical trials driven by the development of KA in severely sun-damaged patients seen in one study (LP0105-1020).

In long-term clinical trials which compare ingenol mebutate versus vehicle there is no statistically significant difference in the occurrence of skin malignancies, whatever the duration of follow-up or treatment area surface.

In the 3-year follow-up trial comparing ingenol mebutate to imiquimod, there is a statistically significant difference in the occurrence of skin malignancies between ingenol mebutate and the active control (imiquimod) in the treatment area, but not outside the treatment area.

The frequency of skin malignancies was higher in patients who have more than 8 AK lesions. This is in line with epidemiological data (Berker, 2017), and existing mathematical models (Dodson, 1991). Comparing the data of SCC inside and outside treatment area, it is observed that outside the treatment area in the patient group with more than 8 AK lesions at baseline, the percentage of skin malignancies is comparable across treatment arms, whereas in the patient group with 5-8 AK lesions a

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higher percentage is observed in the ingenol mebutate compared to the imiquimod group. Inside the treatment area this difference is greater, and the percentage of skin malignancies is also higher in the ingenol mebutate arm compared to the imiquimod arm in the patient group with more than 8 AK lesions at baseline. The differences observed in patients with 5-8 AK lesions are challenging to interpret, however they suggest a higher risk of skin malignancies linked with ingenol mebutate use.

In the other active controlled trial, comparing ingenol mebutate to diclofenac, with 17 weeks of follow-up, there was only 1 skin malignancy inside the treatment area, which was in the ingenol mebutate group.

Ingenol disoxate and ingenol mebutate are related esters and are considered to have a similar biological activity. Thus, data from ingenol disoxate are considered relevant for the evaluation of the safety profile of ingenol mebutate.

In ingenol disoxate 8-week vehicle-controlled trials, there is no statistically significant difference of occurrence of skin tumours between ingenol disoxate and vehicle.

In ingenol disoxate 14-months vehicle-controlled trials, there is a statistically significant difference of occurrence of skin tumours between ingenol disoxate and vehicle (p=0.005) with a risk difference of 4.9% (95% CI: 2.5%, 7.3%) when compared to vehicle. This is driven by FCC, Bowen's disease, and SCC. The Kaplan-Meier curves begin to separate at month 5. There is no indication of a dose-response relation.

Moreover, there is a statistically significant difference in the occurrence of skin tumours between ingenol disoxate and vehicle in the observational explorative study LP0084-1369, a 2-year follow-up extension of 4 phase 3 trials (p=0.014).

With regards to the interaction by application site, the trial LP0041-63 suggests a larger relative risk (ingenol mebutate vs. comparator) of skin malignancies in subjects treated on the face, than in subjects treated on the scalp; however, the four 14 months follow-up ingenol disoxate trials suggest the opposite interaction. None of these associations are, however, statistically significant.

The majority of skin malignancies reported inside treatment area in the LP0041-63 and LP0041-62 studies occurred in patients with Fitzpatrick skin type II (12 in ingenol mebutate group and 3 in imiquimod group). In the LP0041-63, all patients with skin tumour inside treatment area were men, mostly aged 70 or older in ingenol mebutate arm (mean 72.4). This is not unexpected as in the study LP0041-63, over half of the subject had a Fitzpatrick skin classification of Type II (59.9%) and actinic keratosis is known to occur mostly in men with Fitzpatrick I and II skin type. No patients had immunocompromised status (cancer chemotherapy, acquired immune deficiency syndrome, organ transplantation, immunosuppressive treatment). Eleven subjects had history of skin tumour, but information on localisation was not available.

In total 84 post-marketing case reporting 91 skin malignant tumour events were identified in the safety database of the MAH: more than half are SCCs (58) and the rest being keratoacanthoma (8), BCC (8), Bowen's disease (4), atypical fibroxanthoma (4), malignant melanoma (3), lentigo maligna (2), skin cancer (2), neuroendocrine carcinoma of the skin (1) and sarcoma of the skin (1). The majority of the patients are of advanced age (85% of cases report unknown age or above 65), a large number of patients have past medical history of skin malignancy (33% of cases report skin malignancy history, 85% report either present skin malignancy history, or lack of information on skin malignancy history) and they are pre-disposed to sun-damaged skin. The majority of the reported skin malignancies were observed less than 4 months after Picato treatment (61 events, 67%), especially for SCCs 40/57 (70%). This is not unexpected as events are less likely to be spontaneously reported in association to a treatment administered several months ago.

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Overall, no risk factors could be identified from the data available that would allow to discriminate patients into low- or high-risk category for skin tumours specific following ingenol mebutate use.

Assuming no retreatment and acknowledging the potential for under-reporting the reporting rates in the post-marketing setting (3.5 – 4 cases per 100,000 patient-year) would appear to be well below background rates. In the UK in 2016, incidence rates of non-melanoma skin cancer (NMSC), after adjusting for age, were 204.2 per 100,000 person-years (PY) (95% CI: 202.6 – 205.7) in women, and 327.7 per 100,000PY (95% CI 325.5 – 329.8) in men (Cancer Research UK 2019). One study among 918 adults with 10 or more AKs but no previous history of skin cancer estimated incidence rates of 4106 and 3198 per 100 000 person-years, for BCC and SCC, respectively (Foote 2001).

However, data from post-marketing cases is difficult to interpret as elements allowing to determine whether reported skin tumours may be considered to be a manifestation of the risk factors present in the treated population and/or related to treatment with ingenol mebutate are lacking. The most reliable information thus derives from controlled, randomised clinical studies.

A number of hypothesis explaining the imbalance of skin tumours observed in the above-mentioned clinical trials were postulated, however as discussed below, these do not allow to rule out a tumour promoting effect of ingenol mebutate.

While both studies cannot be directly compared, a similar imbalance to that observed in the LP0041-63 trial, was also seen between imiquimod and diclofenac in the LEIDA trial (risk difference: 5.6% [95% CI: 0.7%, 10.7%]) (Gollnick, 2019). Looking at invasive SCC alone, 4 subjects (1.7%) in the imiquimod group and 7 (3.0%) in the diclofenac group developed SCC in the treatment area. This may point to the efficacy of imiquimod rather than to promotion of existing tumours by the comparator, be it diclofenac or ingenol mebutate. Therefore, it has been postulated that the imbalance observed could be the consequence of the potential mechanism of action of imiquimod on SCC. The PRAC noted however that imiquimod is indicated in AK and superficial BCC but not in SCC, in which the efficacy remains to be demonstrated.

It was also postulated that the observed imbalance in skin tumours may be linked to the potential unmasking of SCC lesions by ingenol mebutate. SCC lesions may be pre-existing at the time of topical treatment but not readily recognised as suspicious in the heavily actinically damaged skin, in which suspected or small SCCs may be adjacent to or obscured by AKs (Bettencourt, 2015). Once the AK effectively cleared with ingenol mebutate, the remaining SCC lesion would thus be unmasked. The MAH further supported this hypothesis by the fact that most of reported post-marketing skin malignancies events were identified within the treatment area with a time to onset of less than 4 months. To the MAH it is unlikely that SCCs, which represent the majority of skin malignancy events reported post-marketing, would arise de novo after treatment with Picato, as they assume a slow progression of SCCs. For the same reasons, tumour promoters are agents that over long-term and repeated exposure may lead to progression of a pre-existing tumour, whereas short-term tumour promotion has not been described thus far (Elinav, 2013; Dalgleish, 2006; Shalapour, 2015). The MAH further argued that fast-growing tumours are more indicative of KA than SCCs. SCCs and KAs may be difficult to distinguish clinically and histologically, which may be the explanation of reports of SCCs. The correct histological diagnosis of KA may require considerable expertise, and for medico legal reasons there is a growing tendency to report KA as SCC or 'SCC (KA type)'. An important consequence of the above considerations with regard to occurrence of skin tumours, especially SCCs, after treatment with ingenol mebutate and, indeed any therapy for AK, is that centralised pathology reading is necessary to get a reliable estimate of the incidence. This was also observed in trial LP0105-1020, in which all 11 SCCs were re-classified as KAs. It should be underlined that not all study participants were biopsied in this study, and not all biopsies were centrally reviewed. KAs can develop shortly after any skin therapy that

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directly or indirectly causes inflammation, have a rapid growth phase of 2 to 10 weeks, a stationary phase of similar duration, and a phase of involution that may take 2 months to 1 year.

Moreover, it would appear that in the vehicle-controlled LP0105-1020 and LP0105-1032 trials and the vehicle-controlled ingenol disoxate studies, a history of SCC, BCC, malignant melanoma or other neoplasia in the selected treatment area was not an exclusion criterion. In the uncontrolled ingenol mebutate 500mcg/g trial LP0041-62, 4.4% of patients had a pre-existing malignancy identified on the screening biopsy. Therefore, some lesions detected in the ingenol mebutate arms of LP0105-1020 and LP0105-1032 and the ingenol disoxate arms of the ingenol disoxate studies might have been pre-existing, unrecognised lesions.

Nevertheless, the PRAC considered this justification not entirely supported. Indeed, if an 'unmasking' mechanism is assumed, an increased number of SCCs would be observed in the ingenol mebutate groups compared to the vehicle groups shortly after treatment, which was not the case. In addition, no 'unmasking' effect was observed with other, more effective, AK treatments. Finally, in long-term trials, an increase of skin malignancies in the treatment area was observed after 4 months in the ingenol mebutate or ingenol disoxate groups (1.5% to 5.9%) compared to vehicle or comparator groups (1.1 % to 3.2%). Therefore, despite the inherent limitations of combining results from studies with different methodologies, the PRAC considered that any unmasking effect with ingenol mebutate or disoxate would not explain the imbalance in occurrence of skin tumours between ingenol mebutate compared to vehicle or comparator groups.

The MAH considers that the investigators were likely to be partly unblinded by observation of marked local skin reactions in ingenol treated patients (but not vehicle). Therefore, the MAH postulated that the results may be confounded by a tendency to biopsy lesions that reoccur in the subjects treated with ingenol disoxate, because these lesions are perceived as 'treatment resistant', which routinely elicits biopsy. According to the MAH, this could lead to a detection bias where more biopsies are taken from patients treated with ingenol disoxate than with vehicle, potentially also leading to a higher number of positive findings related to NMSC in the ingenol disoxate group. The PRAC considered that this hypothesis cannot be excluded, however the stimulation of tumour growth by ingenol disoxate could also be an explanation for the observed imbalance.

In addition, the absence of reduction in incidence of skin tumour in the ingenol mebutate arm of the above-mentioned trials compared to vehicle, keeping in mind that skin cancers remain relatively rare events which might be difficult to observe in these trials, is of concern. Taking into account that ingenol mebutate clears the face and the scalp from AK lesions known to be pre-cancerous lesions, fewer skin tumours would be expected in the corresponding trial arms. Whilst the detection bias described above cannot be ruled out, it could also suggest that ingenol mebutate treats some precancerous AK lesions, but also promotes skin tumours.

2.3. Non-clinical aspects

The MAH has performed a critical review of mechanisms by which Picato might lead to rapidly accelerated growth or increased incidence of tumours (Hanahan, 2011). The authors systematically evaluated 10 recognised capabilities called 'Hallmarks' acquired during the multistep development of human tumours, which together encompass all the capabilities needed for a tumour to escape normal cell regulation, grow, invade and metastasise. For each of the 10 hallmarks the MAH has reviewed all existing evidence that ingenol mebutate may have supporting/opposing/no effect on the hallmark. As ingenol mebutate is an activator of protein kinase C (PKC), literature on the effect of PKC on the hallmarks has also been included in the review.

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Experimental evidence unequivocally points towards an anti-tumour-promoting effect of ingenol mebutate on 6 of these hallmarks, except in case of prolonged use (24 hours in culture) for two of these (enabling replicative immortality and inducing angiogenesis) for which the mechanism is possible by downregulation of PKC expression. Extrapolation of prolonged use studied with Picato administration in human is difficult but considering non-clinical data in minipigs which revealed persistence of ingenol mebutate in skin for at least 4 weeks after application, these mechanisms of action cannot be excluded.

There is evidence that ingenol mebutate has no effect on one hallmark (genome instability and mutation). One hallmark (deregulating cellular energetics) has not been studied and thus an effect cannot be excluded there. For 2 hallmarks, 'sustaining proliferative signalling' and 'evading growth suppressors', there is conflicting evidence. There is solid *in vitro* evidence that ingenol mebutate inhibits proliferation, whereas in vivo studies in several species showed acanthosis (diffuse epidermal hyperplasia, a normal physiological response to skin irritation), which was reversible 8-weeks after last administration. This phenomenon was also reported with other inflammation inducing drugs (e.g. imiquimod treatment in mice). Thus, acanthosis is unlikely to give rise to any long term increase in skin cancer growth.

The MAH also conducted a literature review of evidence of any potential carcinogenic effects of ingenol mebutate high-occupancy targets (27 proteins) identified in an *in vitro* study in immortalised human cell lines (Parker, 2017). Of note, the existence and nature (inhibitory, stimulatory, equivocal) of any interactions between ingenol mebutate and these proteins is purely theoretical as they have not been demonstrated in vivo or in cell culture in vitro. An additional potential target for ingenol mebutate, CACT, was also investigated. Overall, CACT was concluded not to play a significant role in skin cancer development and none of the potential ingenol mebutate high-occupancy targets identified by Parker and colleagues were found to impose a risk for developing NMSC in patients treated topically with Picato.

In addition, results from requested *in vitro* colony formation and migration studies in keratinocytes and SCC cell lines suggested that in all cell types (healthy keratinocytes, patient-derived AK cells, human SCC cell lines) migration was either inhibited or unaffected by ingenol mebutate when compared to control. This conclusion is based on one experiment only.

Results from requested *in vitro* colony formation and migration studies immortalised AK cell line were inconsistent so far.

Overall, no clear mechanism of action of ingenol mebutate in tumour development was identified. A role of PKC activation/downregulation of PKC expression in promoting tumours cannot be ruled out based on available data.

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2.4. Data on efficacy

2.4.1. Data on the established efficacy of Picato

The clinical efficacy of ingenol mebutate in the authorised indication had been established during the initial marketing authorisation application based on the assessment of data from 4 clinical trials (PEP005-014, -016, -025, -028).

Table 23. Rates of subjects with complete and partial clearance and median percent (%) lesion reduction in actinic keratosis at day 57 (Picato product information)

	Face and scalp		Trunk and extremities	
	Picato 150 mcg/g (n=277)	**Vehicle (n=270)**	**Picato 500 mcg/g (n=226)**	**Vehicle (n=232)**
Complete Clearance Rate[a]	42.2%[d]	3.7%	34.1%[d]	4.7%
Partial Clearance Rate[b] (≥ 75%)	63.9% [d]	7.4%	49.1% [d]	6.9%
Median % Reduction[c]	83%	0%	75%	0%

[a] Complete clearance rate was defined as the proportion of patients with no (zero) clinically visible actinic keratosis lesions in the treatment area.
[b] Partial clearance rate was defined as the percentage of patients in whom 75% or more of the number of *baseline* actinic keratosis lesions were cleared.
[c] Median percent (%) reduction in actinic keratosis lesions compared to *baseline*.
[d] p<0.001; compared to vehicle by logistic regression with treatment, study and anatomical location.

In addition, efficacy at 12 months was established in three prospective, observational long term 1-year follow-up studies (PEP005-030, -031, -032). Only those patients who achieved complete clearance in the treated area at day 57 of the above-mentioned studies were eligible for long term follow-up.

Table 24. Rate of recurrence of actinic keratosis lesions at 12 months (Picato product information)

	Picato 150 mcg/g gel Face and scalp (n=108)	**Picato 500 mcg/g gel Trunk and extremities (n=76[c])**
Recurrence Rate 12 months KM estimate (95% CI)[a]	53.9% (44.6-63.7)	56.0% (45.1-67.6)
Lesion Based Recurrence Rate[b] 12 months Mean (SD)	12.8% (19.1)	13.2% (23.0)

[a] The recurrence rate is the Kaplan-Meier (KM) estimate at the target study date of the visit expressed as a percentage (95% CI). Recurrence was defined as any identified actinic keratosis lesion in the previously treated area for patients who achieved complete clearance at day 57 in the previous phase 3 studies.
[b] The lesion-based recurrence rate for each patient defined as the ratio of the number of actinic keratosis lesions at 12 months to the number of lesions at *baseline* in the previous phase 3 studies.
[c] Of these, 38 subjects were previously treated in a vehicle controlled phase 3 study and 38 subjects were previously treated in an uncontrolled phase 3 study.

Finally, efficacy of up to two treatment courses at 3 and 12 months was established in a double blind, vehicle-controlled study. Patients, in whom a first treatment course did not lead to complete clearance of all AKs in the treatment area after 8 weeks, were randomised to another treatment course with Picato or vehicle. Patients in whom the first treatment course led to complete clearance were seen at 26 and 44 weeks and randomised to a second treatment course if they had a recurrence in the field. The first treatment course, given open label, resulted in a complete clearance rate of 62% (277/450). The results of the randomised and blinded second treatment course are presented in the below table.

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Table 25. Complete clearance[a] of the field 8 weeks after randomisation and Month 12 (Picato product information)

	Field recalcitrant[c]		Field recurrent[d]	
	Picato 150 mcg/g gel (n= 92)	Vehicle (n=49)	Picato 150 mcg/g gel (n=42)	Vehicle (n=20)
8 weeks after randomisation	47% (43) (p=0.001[b])	18% (9)	60% (25) (p=0.013[b])	25% (5)
Month 12	18% (17) (p=0.016[b])	4% (2)	31% (13) (p=0.10[b])	15% (3)

[a] Complete clearance rate is defined as the proportion of patients with no (zero) clinically visible actinic keratosis lesions in the treatment area.
[b] Cochran-Mantel-Haenszel test of Picato® gel 150 mcg/g compared to vehicle adjusted for anatomical location (face/scalp) and country.
[c] Patients, in whom the first treatment course did not lead to complete clearance of all AKs in the treatment area.
[d] Patients in whom the first treatment course did lead to complete clearance and who had a recurrence in the treatment area at either week 26 or 44.

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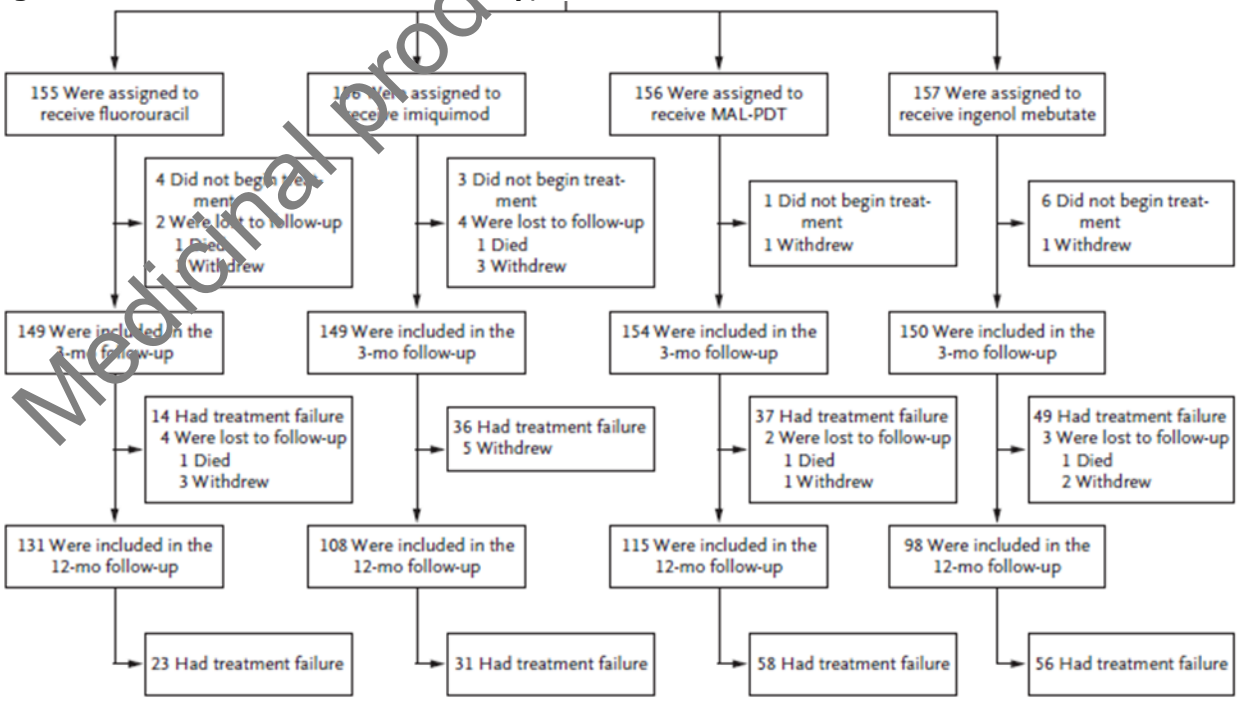
2.4.2. New data on the efficacy of Picato

The results of a multicentre, single-blind, randomised trial comparing the efficacy and safety of ingenol mebutate to 3 other treatments for actinic keratosis were recently published (Jansen, 2019). A total of 624 patients were randomly assigned in a 1:1:1:1 ratio to 5% fluorouracil cream, 5% imiquimod cream, methyl aminolevulinate photodynamic therapy (MAL-PDT), or 0.015% ingenol mebutate gel. The treatment strategy allowed for a second treatment in case of insufficient treatment response, defined as a lesion response of less than 75% at the first follow-up visit. In case of less than 75% clearance of actinic keratosis 3 months after the final treatment, those patients were assessed as having treatment failure for the final analysis.

Figure 13. Randomisation and follow-up, Jansen 2019



A modified intention-to-treat analysis was based on 602 randomly assigned patients who started treatment and for whom data regarding the primary outcome were available.

Figure 14. Cumulative probability of treatment success at 3 and 12 months after the end of treatment and hazard ratios for treatment failure, Jansen 2019

Table 2. Cumulative Probability of Treatment Success at 3 and 12 Months after the End of Treatment and Hazard Ratios for Treatment Failure.*

Variable	Treatment Success		Cumulative Probability of Remaining Free from Treatment Failure (95% CI)†		Hazard Ratio (95% CI)	P Value‡
	3 Mo after End of Treatment	12 Mo after End of Treatment	During 3 Mo after End of Treatment	During 12 Mo after End of Treatment		
	number/total number (percent)		*percent*			
Modified intention-to-treat population						
Fluorouracil	135/149 (90.6)	108/131 (82.4)	90.6 (84.7–94.3)	74.7 (66.8–81.0)	1.00	
Imiquimod	113/149 (75.8)	76/107 (71.0)	75.8 (68.1–81.9)	53.9 (45.4–61.6)	2.03 (1.36–3.04)	0.001
MAL-PDT	117/154 (76.0)	57/115 (49.6)	76.0 (68.4–82.0)	37.7 (30.0–45.3)	2.73 (1.87–3.99)	<0.001
Ingenol mebutate	101/150 (67.3)	42/98 (42.9)	67.3 (59.2–74.2)	28.9 (21.8–36.3)	3.33 (2.29–4.84)	<0.001
Per-protocol population						
Fluorouracil	137/147 (93.2)	109/133 (82.0)	93.2 (87.7–96.3)	76.4 (68.6–82.5)	1.00	
Imiquimod	109/135 (80.7)	73/104 (70.2)	80.7 (73.0–86.5)	56.7 (47.7–64.7)	2.03 (1.33–3.10)	0.001
MAL-PDT	114/137 (83.2)	57/112 (50.9)	83.2 (75.8–88.5)	42.4 (33.9–50.5)	2.63 (1.76–3.94)	<0.001
Ingenol mebutate	102/136 (75.0)	42/99 (42.4)	75.0 (66.8–81.4)	31.8 (24.1–39.8)	3.33 (2.25–4.94)	<0.001

* Because the fluorouracil group had the highest rate of treatment success, it was used as the reference group, according to the statistical analysis plan. CI denotes confidence interval.
† Cumulative probabilities were based on Kaplan–Meier analysis.
‡ P values were based on Cox regression analysis.

2.4.3. Discussion on Efficacy

The efficacy of Picato was previously assessed as follows:

- rate of success at 2 months (defined as the percentage of patients in whom 75% or more of the number of baseline actinic keratosis lesions were cleared): 63.9%;
- rate of recurrence at 12 months (defined as any identified actinic keratosis lesion in the previously treated area for patients who achieved complete clearance at day 57): 53.9%.

In the recently published study, the rate of success of Picato is 67.3% at 3 months and 42.9% at 12 months. It further supports that the efficacy of Picato is moderate and not maintained in time as treatment failure was reported in 57.1% of the patients at 12 months, despite allowing for a retreatment in case of insufficient response. Further, it shows that it has the lowest efficacy of all four treatment options (42.9% for Picato at 12 months versus 49.6% for MAL-PDT, 71% for imiquimod and 82.4% for fluorouracil).

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3. Benefit-risk balance

Picato (ingenol mebutate) was authorised in the EU under the centralised procedure in November 2012 for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) in adults. Left untreated AK may progress to skin malignancies. Picato 150 micrograms/gram gel is used on the face and scalp while Picato 500 micrograms/gram gel is used on the trunk and extremities. However, ever since the initial marketing authorisation application evaluation, there have been concerns that Picato may induce skin tumours. At time of the initial marketing authorisation the conduct of a trial was therefore imposed on the MA to investigate the long-term risk of SCC compared to imiquimod (LP0041-63).

PRAC considered the final safety data of this study as well as a cumulative review of all cases of skin tumours in clinical trials with ingenol mebutate and data on skin tumours from randomised clinical trials with ingenol disoxate and from post-marketing reports. PRAC also considered non-clinical data on

mechanisms by which Picato might lead to rapidly accelerated growth or increased incidence of tumours. In addition, efficacy data from a recently published trial was considered in the context of the known efficacy of Picato (Jansen, 2019).

The statistically significant imbalance in the occurrence of skin malignancy, especially squamous cell carcinoma (SCC), between ingenol mebutate and the active control (imiquimod) observed in the interim results of the LP0041-63 trial is confirmed in the final results (21 cancers versus 6), which is of major concern. While the MAH suggests this might be explained by an intrinsic efficacy of imiquimod, an alternative possibility is that Picato fails to prevent malignancies, either because it promotes skin malignancies, or because it does not lead to the expected goal of preventing the development of skin malignancies, despite its moderate action on actinic keratosis. In addition, imiquimod is not indicated for the treatment of SCC, in which its efficacy remains to be demonstrated. While an imbalance was also observed between diclofenac and imiquimod in the LEIDA trial (Gollnick, 2019), the imbalance was more limited and the time to onset is less suggestive as the difference between the two arms appeared at a later stage. In addition, both trials cannot be directly compared. In the ingenol mebutate arm of trial LP0041-63, skin malignancies occurred in male patients age around 70, mostly with Fitzpatrick skin type II. No patients had an immunocompromised status.

There was a statistically significant imbalance in the occurrence of skin tumours between ingenol disoxate and vehicle in a pooled analysis of four 14-months trials, with a risk difference of 4.9% (95% CI: 2.5%, 7.3%). This is driven by BCC, Bowen's disease, and SCC. Ingenol disoxate, structurally closely related to ingenol mebutate, is considered to have a similar biological activity to that of ingenol mebutate, and its safety profile is considered relevant to characterise that of Picato. The MAH postulated that the results may be confounded by a tendency to biopsy lesions that reoccur in the subjects treated with ingenol disoxate, because these lesions are perceived as 'treatment resistant', which routinely elicits biopsy. This hypothesis cannot be excluded, however the stimulation of tumour growth by ingenol disoxate could also be an explanation for the observed imbalance.

In 8-week follow-up vehicle-controlled clinical trials with ingenol mebutate in 25 cm^2 treatment areas, there was no significant difference in the occurrence of skin tumours. However, when considering a larger treatment area there is a statistically significant difference in a pooled analysis of three clinical trials driven by the development of KA in severely sun-damaged patients seen in the LP0105-1020 trial. In long term vehicle-controlled clinical trials, no significant difference in the occurrence of skin malignancy was observed, whatever the duration of follow-up or treatment area surface. Acknowledging that skin cancers remain relatively rare events which might be difficult to observe in this context, the clearance of AK lesions known to be pre-cancerous by ingenol mebutate would be expected to reduce the occurrence of skin cancers compared to the vehicle arm. Whilst the detection bias described above cannot be ruled out, the absence of such effect could also suggest that ingenol mebutate treat some precancerous AK lesions, but also promotes some skin tumours.

It was also postulated that the observed imbalance in skin tumours may be linked to pre-existing SCC lesions unmasked once the AK effectively cleared with ingenol mebutate. However, if this mechanism is assumed, an increased number of SCCs would be observed in the ingenol mebutate groups compared to the vehicle groups shortly after treatment, which was not the case. In addition, no 'unmasking' effect was observed with other, more effective, AK treatments. Finally, despite the inherent limitations of combining results from studies with different methodologies, an increase of skin malignancies in the treatment area was observed after 4 months in the ingenol mebutate or ingenol disoxate groups compared to vehicle or comparator groups. Therefore, the PRAC considered that any unmasking effect would not explain the imbalance in occurrence of skin tumours.

Post-marketing surveillance consistently reported increasing numbers of skin cancers, especially SCC. Cumulatively, 84 skins cancers are reported. The majority of the reported skin malignancies were

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observed less than 4 months after Picato treatment, especially for SCC. Whilst patient exposure was not estimated, considering the estimated 2.8 million treatment courses administered, this does not appear superior to known background rates for these conditions. However, data from post-marketing cases is difficult to interpret due to protopathic bias. In addition, it is less likely that events would be reported in association with a treatment that was administered several months ago. Thus, the most reliable information derives from randomised controlled trials.

Overall, no risk factors could be identified from the data available that would allow to discriminate patients into low- or high-risk category for skin tumours specific following ingenol mebutate use.

Based on the chemical structure of ingenol mebutate it cannot be excluded that it may have pro-tumourigenic properties. While no clear mechanism could be identified at present for a tumour promoting effect of ingenol mebutate, protein kinase C (PKC)/down-regulation of PKC expression could not be ruled out.

In this context, it is also noted that a recently published study provides further evidence on the level of efficacy of Picato at 3 months (67.3% clearance) and at 12 months (42.9% clearance). A high recurrence rate is observed. PRAC noted that in this study the efficacy of Picato is lower to that of 3 alternative treatments (photodynamic therapy (MAL-PDT), imiquimod and fluorouracil). The authors noted that no unexpected toxic events were reported. While it is acknowledged that the study was likely not powered to evaluate malignancy, based on the incidences reported in the clinical trials in which malignancies have been observed with ingenol, cases of malignancy might have been expected. In addition to photodynamic therapy, imiquimod, fluorouracil and diclofenac, the PRAC noted that in case of isolated lesions cryotherapy, curettage, excisional surgery constitute effective alternative options to ingenol mebutate.

The PRAC noted that some uncertainty remains regarding the possible effect of detection bias, of unmasking of SCC, of the activity of imiquimod on the finding of LP0041-63, regarding the retention time in human skin and the mechanism for a tumour promoting effect of ingenol. However, as explained above, none of these possible effects would suffice to explain the observed imbalance in skin tumours.

The PRAC also evaluated if measures would allow to minimise the risk to an acceptable level. However, based on the data available, the PRAC could not identify such measures or a patient population in which the balance of benefits and risks would be more favourable.

Taking into account the serious concerns regarding a risk of skin tumour in the treatment area associated to Picato, including the final results of study LP0041-63, that no appropriate risk minimisation measures could be identified and noting the recent publication of results further supporting that the efficacy of Picato is not maintained over time, the PRAC considered the benefit-risk balance of Picato unfavourable in its authorised indication.

The PRAC noted the challenges expressed by the scientific advice working party when reviewing a randomised controlled trial protocol proposed by the MAH to further explore the risk of skin malignancy and question whether it would be feasible owing to the very large sample size that would be needed. The PRAC considered that due to the inherent limitations to the design, non-randomised studies would not provide meaningful data on the concerns at stake.

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4. Risk management

The Committee, having considered the data submitted in the procedure was of the opinion that risk minimisation measures cannot reduce the risks to an acceptable level.

5. Grounds for recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004, resulting from pharmacovigilance data, for Picato (ingenol mebutate).
- The PRAC reviewed all the information available, from clinical trials, post-marketing reports and non-clinical studies, on the risk of skin tumours in the treatment area in patients treated with Picato (ingenol mebutate).
- The PRAC considered that the evidence on the risk of skin malignancies with ingenol mebutate from all the available data, including the statistically significant imbalance in skin malignancies with ingenol mebutate compared to imiquimod confirmed in the final study results of trial LP0041-63, raised serious safety concerns.
- The PRAC also noted study results supporting the previously observed decreasing efficacy of Picato over time.
- The PRAC could not identify measures to minimise the risk of skin tumours in the treatment area to an acceptable level.
- The PRAC could not identify any sub-group of patients in which benefit from treatment with Picato would outweigh its risks.

The Committee, as a consequence, considers that the benefit-risk balance of Picato (ingenol mebutate) is not favourable.

The PRAC noted the Commission Decision withdrawing the marketing authorisation of Picato at the MAH's request issued on 11 February 2020.

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