Dermatology beyond the skin

Cover Page

Official title: Risk of Squamous Cell Carcinoma on Skin Areas Treated With Ingenol Mebutate Gel, 0.015% and Imiquimod Cream, 5%
LEO Pharma number: LP0041-63
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CONFIDENTIAL

Statistical Analysis Plan

Risk of Squamous Cell Carcinoma on Skin Areas Treated with Ingenol Mebutate Gel, 0.015% and Imiquimod Cream, 5%

A phase 4 trial comparing the cumulative incidence of SCC after treatment with ingenol mebutate and imiquimod for multiple actinic keratoses on face and scalp

A multi-centre, randomised, two-arm, open label, active-controlled, parallel group, 36-month trial

LEO Pharma A/S	**Trial ID:**	**LP0041-63**
	Date:	**28-AUG-2019**
	Version:	**Final 1.0**

1 Statistical Analysis Plan Approval

1.1 Approval Statement

On behalf of LEO, the Biostatistics Lead and the Vice President of Medical Science, are authorised to approve the Statistical Analysis Plan.

The QC statistician has by approving this document confirmed that the statistical information has been subject to statistical quality control.

The following persons have approved this Statistical Analysis Plan using electronic signatures as presented on the last page of this document.

PPD .

Biostatistics Lead, Global Clinical Operations

PPD

Vice President, Medical Science

PPD

QC Statistician, Biostatistics

2 Statistical Analysis Plan Statements

2.1 Compliance with Good Clinical Practice

This Statistical Analysis Plan is designed to comply with the standards issued by the International Conference on Harmonisation (ICH) (E3: Structure and Content of Clinical Study Reports, E6: Good Clinical Practice, and E9: Statistical Principles for Clinical Trials).

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3 List of Abbreviations

3.1 List of Abbreviations

AE	Adverse Event
AK	Actinic Keratosis
ATC	Anatomical Therapeutic Chemical
BCC	Basal Cell Carcinoma
CCTP	Consolidated Clinical Trial Protocol
CI	Confidence Interval
CM	Concomitant Medication
DK	Denmark
FAS	Full Analysis Set
ICH	International Conference on Harmonisation
LSR	Local Skin Response
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
PT	Preferred Term
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SE	Standard Error
SMQ	Standardised MedDRA Query
SOC	System Organ Class
WHODD	WHO Drug Dictionary

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5 Introduction

The statistical analysis will be performed as outlined in the Consolidated Clinical Trial Protocol (CCTP). This Statistical Analysis Plan contains a more technical and detailed elaboration of some points in the statistical analysis section in the CCTP.

6 Trial Analysis Sets

The full analysis set (FAS) is defined as all randomised subjects.

The safety analysis set is defined as all subjects who receive an initial study treatment and have safety data available.

The per protocol (PP) analysis set will be used as safety and efficacy subsets and is defined as subjects in the FAS who complete the trial without major protocol deviations affecting the primary and secondary safety and efficacy endpoints. Censoring as well as a full exclusion from the PP analysis set will be used in the primary analysis and in all other time-to-event analyses. A subject who is to be excluded from the PP analysis set will be in the analysis until the subject is censored at the time the event leading to exclusion from PP occurs in time-to-event analyses in case the event occurs after Day 1. This is in line with estimands defined by the composite strategy in ICH E9 (R1) addendum on estimands (1).

Please see the Analysis Set Definition Document for details.

7 Statistical Analysis

Please see section 7.5 for general principles.

7.1 Baseline Considerations

Baseline is defined as the last assessment prior to administration of trial medication.

7.1.1 Disposition

Summary of subject disposition will be presented with the number of randomised, withdrawn, and completed subjects, and frequencies of the analysis sets, in total and by treatment group. Reasons for withdrawal from the trial and premature discontinuations by last visit attended will be presented for the safety analysis set.

Enrolled subjects by country and site will be presented.

7.1.2 Baseline Characteristics and Demographics

Descriptive statistics of demographic and other baseline characteristics will be presented for the safety analysis set.

Demographics will include age, sex, race, ethnic origin, and skin types. Other baseline characteristics will include height, weight, BMI, vital signs, other diagnoses, and concomitant medication (CM). Baseline Actinic Keratosis (AK) characteristics will include anatomical location (face or scalp) and baseline AK count.

Medical history will be summarised by System Organ Class (SOC) and Preferred Term (PT). AK treatment history and history of Squamous Cell Carcinoma (SCC) will be summarised.

For reporting in clinical trial data registries, age group (18-64, 65-84, ≥85) will be summarised for all randomised subjects, and age and sex will be summarised for the FAS, safety analysis set, and PP analysis set.

7.2 Exposure and Other Dosing Information

Exposure and other dosing information will be presented for the safety analysis set.

7.2.1 Exposure

The number of treatment cycles received will be presented by country, by anatomical location and by history of SCC.

7.2.2 Compliance

Compliance will be summarised by country and visit, and by visit.

7.2.3 Drug Accountability

The number of used and unused tubes returned will be listed.

7.2.4 Concomitant Medication and Procedures

CM is coded using WHO Drug Dictionary (WHODD) version 2012Q1.
CM at baseline will be summarised by anatomical location and Anatomical Therapeutic Chemical (ATC) level 1 and 4.

Concomitant procedures at baseline will be summarised by anatomical location.

7.3 Analysis of Safety

All safety analyses will be carried out using the safety analysis set unless otherwise stated.

7.3.1 Censoring

Since the primary and secondary safety criteria are time-to-event analyses, a censoring scheme will be defined. This is not detailed in the CCTP.

Subjects from the safety analysis set will be included in the time-to-event analyses, as described in Table 1:

Table 1: Censoring

Event	Date	Outcome
SCC	Date of biopsy	Event
Missing result from a biopsy	Date of biopsy	Censored
Trial completion without SCC	Date of last visit with assessment and no SCC	Censored
Trial discontinuation	Date of last visit with assessment and no SCC	Censored
Death from any cause	Date of death	Censored

SCC: Squamous cell carcinoma

In addition, a PP censoring will be defined, which is censoring at the time when a subject is excluded from the PP analysis set, as described in Table 2:

Table 2: PP censoring

Event	Date	Outcome
Exclusion from PP analysis set with no documented SCC	Date of last visit with assessment before exclusion with no SCC	Censored

PP: Per protocol, SCC: Squamous cell carcinoma

Details on censored subjects are given by subject ID in the analysis set definition document.

7.3.2 Primary Safety Criterion

The primary safety criterion is diagnosis of SCC (defined as invasive SCC, i.e. excluding SCC in situ) in the treatment field across the 3-year trial period. Invasive SCC is diagnosed by biopsy.

The CCTP states: "*The 3-year cumulative incidence will be calculated for each treatment group using methods of survival analysis for estimation of cumulative incidence in the presence of censored time-to-event data. Annual incidence rates will also be presented for each group. The cumulative incidence rates will be presented for the event of SCC as primary endpoint and for SCC and other neoplasia as secondary. No formal statistical test comparing the two arms will be performed. For descriptive purposes, as an additional analysis, the difference in cumulative incidence rates between the two arms will be estimated and presented together with its 95% confidence interval.*"

The time to first SCC in months will be calculated as days divided by the average number of days in a month:

(Date of biopsy - date of first exposure to trial medication)/30.4375

The cumulative incidence rate with 95% confidence intervals (CIs) will be estimated for each treatment group using SAS *PROC LIFETEST* where the *STRATA* statement will include the randomisation stratification factors *country, anatomical location, and history of SCC*, and with the option *GROUP=treatment*. The incidence rates will be presented using the option *TIMELIST=12 24 36* for 1, 2 and 3 years, respectively. Cumulative incidence will be presented by 1 minus the survival curves estimated using the Kaplan-Meier method. Moreover, numbers at risk and censoring information will be presented by treatment group.

The analysis will be presented for the safety analysis set. In addition, the analysis will be presented for the PP analysis set using PP censoring as described in section 7.3.1. Please see the analysis set definition document for details.

The additional analysis of difference in the 3-year cumulative incidence rates will be calculated as the difference between the Kaplan-Meier estimates of each treatment group and will be presented with 95% CI. The difference is assumed to be approximately normally distributed, and as the treatment groups are assumed to be independent and identically distributed, the 95% CI will be calculated as $\pm 1.96 \times \sqrt{(SE_{Ing}^2 + SE_{Imi}^2)}$ where SE_{Ing} and

SE_{Imi} are the standard errors (SEs) of the Kaplan-Meier estimates in the ingenol mebutate and imiquimod groups, respectively.

Suspicion of SCC or other neoplasia (Yes/No) will be summarised by visit. The results of biopsies will be summarised by visit and by country.

7.3.3 Secondary Safety Criterion

The secondary safety criterion is diagnosis of SCC and other neoplasia in the treatment field over a 3-year period and will be analysed like the primary safety endpoint.

SCC and other neoplasia are diagnosed by biopsy and include the following diagnoses

- Invasive SCC
- Basal Cell Carcinoma (BCC)
- In Situ BCC/Bowen
- Other neoplasia

The diagnoses "Actinic Keratosis" and "No malignant findings" are not neoplasia events.

The analysis will be presented for the safety analysis set. In addition, the analysis will be presented for the PP analysis set using PP censoring. Please see the analysis set definition document for details.

The CCTP states

"A landmark analysis, conditional on patients' responses at Week 20, will additionally be performed in order to exclude SCC and other neoplasia reported within the first 20 weeks which are not assumed to be associated with the study treatment. Patients who experience a neoplasia before the 20-week landmark time point are excluded from the time-to-event analysis, which is otherwise conducted as above."

Diagnosis of SCC and other neoplasia in the treatment field from Week 20 onward will be analysed as described above.

7.3.4 Other Safety Criteria

Physical examination will be summarised by visit.

7.3.5 Adverse Events

Adverse events (AEs) will be presented as described in the CCTP.

An AE will be considered treatment emergent if the event emerges during treatment having been absent pre-treatment or worsens relative to the pre-treatment state. This is as defined in ICH E9.

Skin malignancies inside the treatment area are defined using Medical Dictionary for Regulatory Activities (MedDRA) v 15.1 as AEs from the Standardised MedDRA Query (SMQ) *skin malignant tumours.* Skin malignancies inside the treatment area will be presented by PT.

7.3.6 Local Skin Responses

Local Skin Responses (LSRs) will be presented as described in the CCTP.

7.3.7 Laboratory Data

Urine pregnancy test data will be listed.

7.4 Analysis of Efficacy

All efficacy analyses will be carried out for the FAS and the PP analysis set unless otherwise stated.

7.4.1 Efficacy Criteria

The efficacy criteria as defined in the CCTP are the following secondary criteria

- Complete AK clearance after the last treatment cycle (at Week 8 or 16)
- Partial (at least 75%) AK clearance after the last treatment cycle (at Week 8 or 16)
- Complete AK clearance at 12 months, defined as no AKs in the selected treatment area at any time from the last treatment cycle at Week 8 or 16 through to Month 12.

The criteria will be analysed as described in the CCTP.

Complete and partial clearance will be summarised by visit with 95% CI of clearance percentage.

Percent reduction in AK count will be summarised by visit.

7.5 General Principles

7.5.1 Statistical Analysis

In general, all output will be presented by treatment group where nothing else is mentioned. Descriptive statistics for all endpoints will be presented by treatment group and visit (if applicable) using observed cases, i.e. no imputation of missing data will be performed. Summaries by subgroup will include presentation of the endpoint in question by subgroup and overall.

Continuous data will be presented using the number of subjects, mean, standard deviation (SD), median, minimum, and maximum as described in the protocol. In addition, lower and upper quartile will be presented. Both the absolute values and the relative change from baseline will be presented.

Statistical tests will be performed as described in the protocol unless otherwise detailed.

Medical history and AEs are coded using MedDRA version 15.1.

7.5.2 Pooling of Trial Sites

There will be no pooling of trial sites.

7.5.3 Handling of Drop-outs and Missing Values

Drop-outs will be handled as described in section 7.3.1 for the primary and secondary safety criteria using censoring in time-to-event analyses.

Missing results from biopsies will be handled using censoring as described in section 7.3.1.

Besides this, no imputation will be implemented.

7.5.4 Incomplete Dates

The following rules apply for incomplete dates.

Adverse events

- AE start day is missing but not AE start month and year:
    - If the year and month of AE start is before the year and month of exposure start, or if AE end date is complete and before exposure start, then the AE will not be considered treatment emergent.

- If the year and month of AE start is the same as the year and month of exposure start, then the AE will be considered treatment emergent, unless the AE has a complete end date which is before exposure start.
- If the year and month of the AE start is after the year and month of exposure start, then the AE will be considered treatment emergent.

- AE start month is missing but not AE start year:
  - If the year of AE start is before the year of exposure start, or AE end month and year are not missing and are before the month and year of exposure start, or if AE has a complete end date which is before the exposure start date, then the AE will not be considered treatment emergent.
  - If the year of AE start is the same as the year of exposure start, then the AE will be considered treatment emergent, unless the AE end month and year are not missing and are before the month and year of exposure start or AE has a complete end date which is before the exposure start date.
  - If the year of AE start is after the year of exposure start, then the AE will be considered treatment emergent.

Concomitant medication

- Incomplete CM start dates:
  - If the start day is missing but not the start month and year, it will be assumed that the start day is the first day of the month.
  - If the start day and month are missing but not the start year, it will be assumed that the start day is 01 January.
  - If the start day, month, and year are missing, it will be assumed that the medication was started before trial start.

- Incomplete CM end dates:
  - If the end day is missing but not the end month and year, it will be assumed that the end day is the last day of the month.
  - If the end day and month is missing but not the end year, it will be assumed that the end day was 31 December.
  - If the end day, month, and year is missing, it will be assumed that the medication was ongoing at the end of the trial.

7.5.5 Treatment Labels

The following labels will be used for the two treatment groups:

Table 3: Treatment labels for the clinical trial report text and tables

Label Used in Text	Label Used in Tables	Order in Table
Ingenol mebutate	Ingenol mebutate	1
Imiquimod	Imiquimod	2

7.5.6 Changes to the Protocol

- The CCTP states: "*An interim analysis of trial data, obtained when approximately half of the trial period has elapsed, will be conducted. Assuming the time schedule shown in section 10.2, this will be prepared 3 years after study start. The interim analysis will not impact the conduct of this trial*." This interim analysis was not conducted since the Pharmacovigilance Risk Assessment Committee at the European Medicines Agency found that the Periodic Safety Update Report was satisfactory.
- The CCTP states: *"A per protocol (PP) analysis set will be used as safety and efficacy subsets and will be defined as subjects in the FAS who complete the trial without major protocol deviations."* Only deviations having impact on safety or efficacy will be considered. As the primary analysis is a time-to-event analysis, subjects will be censored from the PP analysis at the time of the deviation, i.e. the subject will be in the PP analysis set until the day when the deviation takes place.
- To support the primary endpoint, descriptive statistics of demographic and other baseline characteristics will be presented for the safety analysis set and not for the FAS as described in the CCTP.
- Reason for premature discontinuation from treatment is not presented as it is not captured in the eCRF. Reason for not applying trial medication according to protocol is listed.

7.6 References

1) ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, 2017

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Table shells

Shell 1: Subject disposition: safety analysis set

	Ingenol mebutate (n=xxx)		Imiquimod (n=xxx)		Total (n=xxx)	
	N[1]	(%)	N	(%)	N	(%)
Randomised (FAS[2])	xxx	(xx.x)	xxx	(xx.x)	xxx	(xx.x)
Safety analysis set	xxx	(xx.x)	xxx	(xx.x)	xxx	(xx.x)
Withdrawals	xxx	(xx.x)	xxx	(xx.x)	xxx	(xx.x)
Completers	xxx	(xx.x)	xxx	(xx.x)	xxx	(xx.x)
PP analysis set	xxx	(xx.x)	xxx	(xx.x)	xxx	(xx.x)
Total	xxx	(xxx.x)	xxx	(xxx.x)	xxx	(xxx.x)

1) N: Number of subjects
2) FAS: Full analysis set

Shell 2: History of SCC: safety analysis set

	Ingenol mebutate (n=xxx)		Imiquimod (n=xxx)	
History of SCC[1]	N[2]	(%)	N	(%)
Yes	xxx	(xx.x)	xxx	(xx.x)
Present diagnosis	xxx	(xx.x)	xxx	(xx.x)
Less than 12 month ago	xxx	(xx.x)	xxx	(xx.x)
More than 12 month ago	xxx	(xx.x)	xxx	(xx.x)
No	xxx	(xx.x)	xxx	(xx.x)
Total	xxx	(xxx.x)	xxx	(xxx.x)

1) SCC: Squamous cell carcinoma
2) N: Number of subjects

Shell 3: Exposure – number of treatment cycles by [country/anatomical location/history of SCC]: safety analysis set

Number of treatment cycles by [country/anatomical location/history of SCC]	Ingenol mebutate (n=xxx) N[1]	(%)	Imiquimod (n=xxx) N[1]	(%)
<Subgroup 1>				
1	xxx	(xx.x)	xxx	(xx.x)
2	xxx	(xx.x)	xxx	(xx.x)
<Subgroup 2>				
⋮				
Total				
1	xxx	(xx.x)	xxx	(xx.x)
2	xxx	(xx.x)	xxx	(xx.x)

1) N: Number of subjects

Shell 4: Histological diagnoses of biopsies: safety analysis set

Histological diagnosis	Ingenol mebutate (n=xxx) N[1]	(%)	Imiquimod (n=xxx) N[1]	(%)
Actinic Keratosis	xxx	(xx.x)	xxx	(xx.x)
In Situ SCC/Bowen	xxx	(xx.x)	xxx	(xx.x)
Invasive SCC	xxx	(xx.x)	xxx	(xx.x)
BCC	xxx	(xx.x)	xxx	(xx.x)
Other Neoplasia	xxx	(xx.x)	xxx	(xx.x)
No malignant findings	xxx	(xx.x)	xxx	(xx.x)
Total	xxx	(xxx.x)	xxx	(xxx.x)

1) N: Number of subjects

Shell 5: Incidence of SCC [and other neoplasia] in the treatment area from [baseline/Week 20] to end of trial: [safety/per protocol] analysis set

SCC[1] [and other neoplasia[2]]	**Ingenol mebutate (n=xxx) N[3] (%) E[4]**	**Imiquimod (n=xxx) N[3] (%) E[4]**
[SCC/SCC and other neoplasia[5]]	xxx (xx.x) xx	xxx (xx.x) xx
No SCC [or other neoplasia]	xxx (xx.x) xx	xxx (xx.x) xx
Cumulative incidence (%)	xx.x	xx.x
Lower 95% CI[6] (%)	xx.x	xx.x
Upper 95% CI (%)	xx.x	xx.x

1) SCC: Squamous Cell Carcinoma
2) SCC and other neoplasia include SCC, BCC, and in situ BCC/Bowens
3) N: Number of subjects
4) E: Number of events
5) XXX subject in xxx treatment group had two incidences of SCC [and other neoplasia]
6) CI: Confidence interval

NOTE: If any incidence of other neoplasia exists with details specified in a text field describing the type, then this must be discussed with the medical expert to identify malignant diagnoses

Shell 6: Annual incidence of SCC [and other neoplasia] in the treatment area from baseline to Month 12, 24, and 36: [safety/per protocol] analysis set

SCC[1] [and other neoplasia[2]]	**Ingenol mebutate (n=xxx)**	**Imiquimod (n=xxx)**
Subject years at Month 12	xxx.x	xxx.x
Month 12 cumulative incidence rate (%)	xx.x	xx.x
Lower 95% CI (%)	xx.x	xx.x
Upper 95% CI (%)	xx.x	xx.x
Subject years at Month 24	xxx.x	xxx.x
Month 24 cumulative incidence rate (%)	xx.x	xx.x
Lower 95% CI (%)	xx.x	xx.x
Upper 95% CI (%)	xx.x	xx.x
Subject years at Month 36	xxx.x	xxx.x
Month 36 cumulative incidence rate (%)	xx.x	xx.x
Lower 95% CI (%)	xx.x	xx.x
Upper 95% CI (%)	xx.x	xx.x

1) SCC: Squamous Cell Carcinoma
2) SCC and other neoplasia include SCC, BCC, in situ BCC/Bowens
3) CI: Confidence Interval

NOTE: If any incidence of Other neoplasia exists with details specified in a text field describing the type, then this must be discussed with medical expert to identify malignant diagnoses

Shell 7: Summary of SCC [and other neoplasia] in the treatment area from baseline to end of trial: [safety/per protocol] analysis set

SCC[1] [and other neoplasia[2]]	**Ingenol Mebutate (n=xxx)**	**Imiquimod (n=xxx)**
Incidence rate [2/3]	xx.xx	xx.xx
Number of incidences		
0	x (xx.xx%)	x (xx.xx%)
1	x (xx.xx%)	x (xx.xx%)
2	x (xx.xx%)	x (xx.xx%)
.		
.		
Total	x (xx.xx%)	x (xx.xx%)
Diagnosis		
Invasive SCC	x (xx.xx%)	x (xx.xx%)
BCC	x (xx.xx%)	x (xx.xx%)
.		
.		
Missing	x (xx.xx%)	x (xx.xx%)
Total	x (xx.xx%)	x (xx.xx%)

1) SCC: Squamous Cell Carcinoma
2) SCC and other neoplasia include SCC, BCC, and in situ BCC/Bowens
3) Incidence rate: 100*(number of events/number of patient years)

NOTE: Diagnosis is only for the secondary endpoint

Shell 8: Incidence of SCC [and other neoplasia] by subgroups: [safety/per protocol] analysis set

Number of subjects with SCC[1] [and other neoplasia[2]] by subgroup	Ingenol mebutate (n=xxx) N[3]	n[4]	(%[5])	E[6]	Imiquimod (n=xxx) N[3]	n[4]	(%[5])	E[6]
Anatomical location								
Face	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
Scalp	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
Country								
France	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
Germany	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
United Kingdom	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
Sex								
Male	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
Female	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
Fitzpatrick skin type								
I	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
II	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
III	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
IV	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
History of SCC								
Yes	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx
No	xxx	x	(xx.x)	xx	xxx	x	(xx.x)	xx

1) SCC: Squamous Cell Carcinoma
2) SCC and other neoplasia includes SCC, BCC, and in situ BCC/Bowens
3) N: Number of subjects in subgroup
4) n: Number of subjects with SCC [and other neoplasia] in subgroup
5) %: Percentage of subjects in the subgroup with SCC [and other neoplasia]
6) E: Number of events

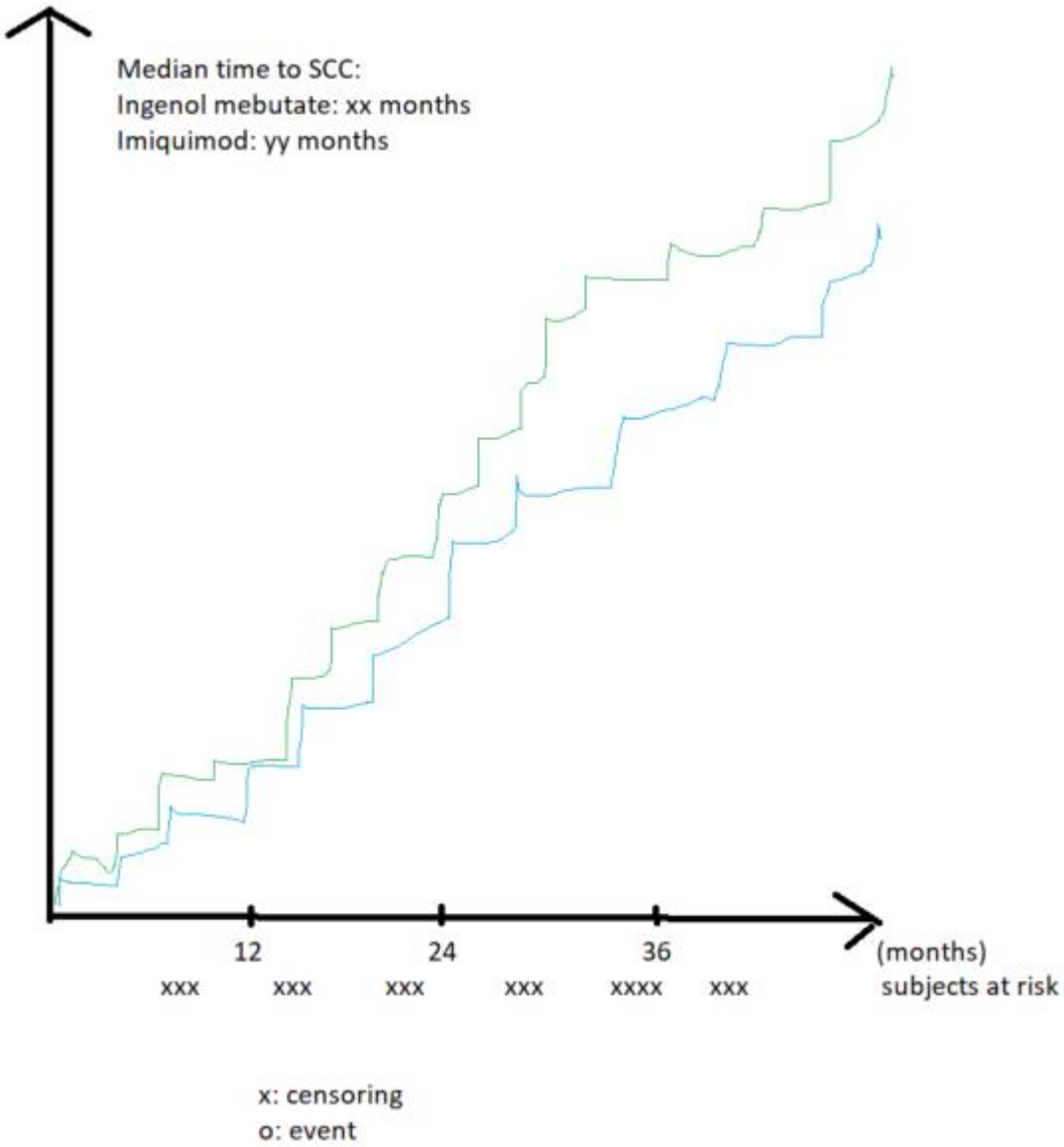
NOTE: Subgroups might change

Shell 9: Difference in incidence of SCC [and other neoplasia] in the treatment area from baseline to Month 36: [safety/per protocol] analysis set

SCC[1] [and other neoplasia[2]]	**Ingenol mebutate (n=xxx)**	**Imiquimod (n=xxx)**
Incidence rate (%)	xx.x	xx.x
Lower 95% CI (%)	xx.x	xx.x
Upper 95% CI (%)	xx.x	xx.x
Difference		xx.x
Lower 95% CI (%)		xx.x
Upper 95% CI (%)		xx.x

1) SCC: Squamous Cell Carcinoma
2) SCC and other neoplasia include SCC, BCC, and in situ BCC/Bowens
3) XXX subject in xxx treatment group had two incidences of SCC [and other neoplasia]
4) CI: Confidence interval

Shell 10: Time to SCC: [safety/per protocol] analysis set



Shell 11: [Complete/Partial] clearance by visit: [full/ per protocol] analysis set

[Complete/Partial[1]] clearance	Ingenol mebutate (n=xxx) N[2]	(%)	Imiquimod (n=xxx) N[2]	(%)
Week 8				
Cleared	xxx	(xx.x)	xxx	(xx.x)
Not cleared	xxx	(xx.x)	xxx	(xx.x)
Total	xxx	(xxx.x)	xxx	(xxx.x)
Lower 95% CL[3] (Cleared)		(xx.x)		(xx.x)
Upper 95% CL[3] (Cleared)		(xx.x)		(xx.x)
Week 16[4]				
Cleared	xxx	(xx.x)	xxx	(xx.x)
Not cleared	xxx	(xx.x)	xxx	(xx.x)
Total	xxx	(xxx.x)	xxx	(xxx.x)
Lower 95% CL[3] (Cleared)		(xx.x)		(xx.x)
Upper 95% CL[3] (Cleared)		(xx.x)		(xx.x)
.				
.				
.				
Month 36				
Cleared	xxx	(xx.x)	xxx	(xx.x)
Not cleared	xxx	(xx.x)	xxx	(xx.x)
Total	xxx	(xxx.x)	xxx	(xxx.x)
Lower 95% CL[3] (Cleared)		(xx.x)		(xx.x)
Upper 95% CL[3] (Cleared)		(xx.x)		(xx.x)

1) Partial clearance: At least 75% reduction in AK count
2) N: Number of subjects
3) CL: Confidence limit
4) Only subjects with two treatment courses attend visit at Week 16

Shell 12: Analysis of [complete/partial] clearance [after the last treatment cycle/at month 12]: [full/ per protocol] analysis set

	Ingenol mebutate (n=xxx)		**Imiquimod (n=xxx)**	
[Complete/Partial[1]] clearance	**N[2]**	**(%)**	**N[2]**	**(%)**
[After last treatment cycle[3,4]/Month 12]				
Cleared	xxx	(xx.x)	xxx	(xx.x)
Not cleared	xxx	(xx.x)	xxx	(xx.x)
Total	xxx	(xxx.x)	xxx	(xxx.x)
Lower 95% CL[5] (Cleared)		(xx.x)		(xx.x)
Upper 95% CL[5] (Cleared)		(xx.x)		(xx.x)
Ratio of clearance rates[6]			xx.xx	
95% CI[7]			xx.xx to xx.xx	
p-value			x.xxx	

1) Partial clearance: At least 75% reduction in AK count
2) N: Number of subjects
3) Last treatment cycle is at Week 8 or Week 16
4) Subjects who were not clear at week 8 and by mistake not entered second treatment cycle are excluded
5) CL: Confidence limit
6) Cochran-Mantel-Haenszel estimate stratified by country, anatomical location and history of SCC
7) CI: Confidence interval

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