Clinical Study Report

Efficacy and Safety of ingenol mebutate gel 0.06% when applied once daily for 2, 3 or 4 consecutive days to a treatment area of approximately 250 cm$^2$ on trunk and extremities in subjects with actinic keratosis

An international, phase 2, randomised, multicentre, double-blind, vehicle-controlled, 8-week trial
Clinical Study Report Statement

Approval Statement, Sponsor

The following persons have approved this Clinical Study Report on behalf of LEO Pharma A/S using electronic signatures:

PPD
PPD Biostatistics

PPD
PPD Medical Department

Approval Statement, Investigator

The international co-ordinating investigator approves the Clinical Study Report by manually signing the International Co-ordinating Investigator Clinical Study Report Approval Form, which is a separate document adjoined to this report.

The following person has approved this Clinical Study Report:

Daniel M. Siegel, MD MS
International co-ordinating investigator
Compliance with Good Clinical Practice
This clinical trial was performed in compliance with GCP, including the archiving of essential documents.

This Clinical Study Report is designed to comply with the standards issued by the International Conference on Harmonisation (ICH) (E3 Structure and Content of Clinical Study Reports and clarified in the ICH E3 Q&A document 07-Jun-2012; E6 Good Clinical Practice; E9 Statistical Principles for Clinical Trials and M4 Common Technical Document) (1, 2, 3, 4, 5).

Public Registration of the Clinical Trial
The trial was registered on Clinicaltrials.gov on 21-Nov-2013, NCT01998984.

Synopsis
The synopsis of this clinical study report exists as a separately approved document.
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LIST OF ABBREVIATIONS
ADR    Adverse drug reaction
AE     Adverse event
AK     Actinic keratosis
ALT    Alanine aminotransferase
AST    Aspartate aminotransferase
BCC    Basal cell carcinoma
CI     Confidence interval
CMO    Contract manufacturing organisation
CRF    Case report form
CRO    Contract research organisation
DMC    Data monitoring committee
DLT    Dose limiting toxicity
FAS    Full analysis set
GCP    Good Clinical Practice
GGT    Gamma-glutamyl transpeptidase
HREC   Human research ethics committee
ICH    International Conference on Harmonisation
ICTM   International Clinical Trial Manager
IEC    Independent ethics committee
IRB    Institutional review board
IWRS   Interactive Web Response System
LLT    Lowest level term
LOCF   Last observation carry forward
LSR    Local skin response
MAR    Missing at random
MI     Multiple imputation
MTD    Maximum Tolerated Dose
MedDRA Medical Dictionary for Regulatory Activities
NLCRA  National Lead Clinical Research Associate
OR     Odds ratio
PP     Per protocol
PT     Preferred term
RDC    Remote data capture
RR     Rate ratios
S(AE)  AE only if no SAE, or AE and SAE
SAE  Serious adverse event
SAPU  Statistical analysis plan update
SCC  Squamous cell carcinoma
SGOT  Serum glutamic oxaloacetic transaminase
SGPT  Serum glutamic pyruvate transaminase
SOC  System Organ Class
SOP  Standard Operating Procedure
STA  Selected treatment area
TEAE  Treatment emergent adverse event
TSQM  Treatment Satisfaction Questionnaire for Medication
WHO  World Health Organisation

DEFINITION OF TERMS

Terms defined by ICH Guidelines are not mentioned here.

Assessment
A (cluster of) characteristic(s) measured and/or recorded for a subject.

Concomitant Medication
Any medication used by a subject during the clinical trial apart from the trial medication.

Enrolled Subject
A subject for who informed consent has been obtained and who has been registered in a clinical trial.

International Clinical Trial Manager (ICTM)
The qualified person appointed by LEO to be the main international sponsor representative responsible for all aspects of a clinical trial as outlined in Global Clinical Operations SOPs.

LEO
LEO (no suffix): refers to the corporate organisation of LEO Pharma A/S.

Monitor
A person appointed by LEO to carry out monitoring of a clinical trial.
**National Lead Clinical Research Associate (NLCRA)**

The person appointed to be the national sponsor representative responsible for all aspects of a clinical trial within a country as outlined in Global Clinical Operations SOPs.

**Randomisation Code List**

A list of (sequential) numbers to each of which a treatment is allocated (assigned). Treatment may be revealed as a code letter (e.g. A, B, …) or by directly revealing the specific treatment (investigational product).

**Response Criterion**

An assessment or a transformation of the assessment(s) described on a subject level, for which a statistical analysis is performed, i.e. a P-value or a confidence interval is stated, or for which tabulation serves as important supportive evidence of efficacy/safety.
1 Ethics

1.1 Human Research Ethics Committee and Institutional Review Board

The clinical study protocol and any relevant amendments to the clinical study protocol were approved by/received favourable opinion from the Institutional Review Boards (IRBs) and Human Research Ethics Committees (HRECs).

The appropriate regulatory authority was notified of the clinical trial, as required.

A list of all IRBs and HRECs consulted is given in Appendix 1.3.

1.2 Ethical Conduct of the Trial

The clinical trial was conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Association General Assembly, 1964, and subsequent amendments.

The clinical trial was conducted in compliance with the clinical study protocol, GCP, and the applicable regulatory requirements.

All subjects received written and verbal information concerning the clinical trial as specified in Section 1.3.

Subjects were asked to consent that their personal data were recorded, collected, processed and could be transferred to EU and non-EU countries in accordance with any national legislation regulating privacy and data protection.

1.3 Subject Information and Informed Consent

All subjects received written and verbal information concerning the clinical trial. This information emphasised that participation in the clinical trial was voluntary and that the subject could withdraw from the clinical trial at any time and for any reason. All subjects were given an opportunity to ask questions and were given sufficient time to consider all relevant issues before consenting.

The subject’s signed and dated informed consent to participate in the clinical trial was to be obtained prior to any trial-related activities being carried out.

A representative subject information sheet and informed consent form is provided in Appendix 1.3.
2 Investigators and Trial Administrative Structure

LEO was the sponsor of the clinical trial and participating LEO affiliates were authorised by the sponsor to act on behalf of the sponsor in the countries where the clinical trial was conducted.

Information on the trial administrative structure as well as the curriculum vitae of the international coordinating investigator and a list of other persons whose participation materially affected the conduct of the trial is included in Appendix 1.4.
3 Introduction

Actinic Keratosis

Actinic keratosis (AK) is a common skin condition visible as thickened, cornified, scaly lesions and characterised histologically by atypical epithelial proliferation (6). Actinic keratoses usually develop on areas that are frequently exposed to the sun (e.g., face, ears, scalp, neck, forearms, and the back of the hands). Patients with AK often express embarrassment, worry, and irritation related to the change in appearance of their skin and unsightly nature of the lesions (7, 8). In addition to the emotional strain, AK lesions can be painful and easily traumatised causing bleeding (8-11).

In population studies performed in the EU and US, reported prevalence rates for AK have been approximately 11-25% of the population, while estimates are higher in Australian studies (up to 60%) (12). Patients with AK tend to have Fitzpatrick type I or II skin (fair skin) which burns with sun exposure and does not tan (10).

In the context of AK, field cancerisation is characterised by the epithelial surface of the photodamaged area being susceptible to the development of additional AKs or a malignancy. This is evidenced by the presence of multiple subclinical and clinically visible AK lesions as well as multifocal pre-neoplastic changes with genetic mutations (13). There is also increasing evidence that AK represents SCC in situ in its earliest stages (6, 14, 15). Histological evidence shows that contiguous AK is present in 97% of SCC lesions on sun-damaged skin (14). Actinic keratosis is linked epidemiologically to development of SCC (16), and both conditions share specific gene expression (17). If left untreated, AK may progress to SCC, with significant morbidity and death (14).

Investigational Product

Ingenol mebutate was identified as the principal active component responsible for the selective cytotoxic effects of *E. peplus* sap, based on its antitumour effects both in vitro and in vivo (18). The mechanism of action in AK remains to be fully characterised. In vivo and in vitro models have shown a dual mechanism of action for the effects of ingenol mebutate: 1) induction of local lesion cell death, and 2) promotion of an inflammatory response characterised by local production of proinflammatory cytokines and chemokines and infiltration of immunocompetent cells (19-25). This mechanism of action distinguishes ingenol mebutate from other therapeutic options and provides a rationale for substantially shorter durations of treatment (2 to 3 days) compared to other approved topical AK products. A clinical development program has investigated the efficacy and safety of ingenol mebutate gel 0.015% in a 3-day regimen on the face and scalp and ingenol mebutate gel 0.05% in a 2-day regimen on the trunk and extremities for the treatment of AK in an area of 25 cm².
Ingenol mebutate gel (0.015% and 0.05%) is approved for treatment of areas up to 25 cm$^2$ in size in US, EU and several other countries under the trade name Picato®.

**Rationale for this Trial**

Actinic keratosis is, however, a disease which often affects larger areas of skin. Therefore a product is needed to treat larger areas such as the full face, full balding scalp, the back of the hand and arm, legs or areas of the trunk.

Part I of a dose-escalation and efficacy clinical trial investigating ingenol mebutate gel for the treatment of AK on full face, full balding scalp or approximately 250 cm$^2$ on the chest (Trial LP0105-1012) was finalised before the present trial LP0105-1020 was initiated. The aim of Part I of trial LP0105-1012 was to establish the Maximum Tolerated Doses (MTD) for ingenol mebutate gel following 2 or 3 days of application to the full face, full balding scalp or approximately 250 cm$^2$ on the chest. Data from part I identified 0.027% as the MTD for a 3-day regimen on the face and 0.06% as the MTD for a 2-day regimen. The safety profile seen in part I of this trial was similar to the safety profile known from using ingenol mebutate gel on a treatment area of 25 cm$^2$. However, the highest concentration investigated in this trial (0.06%) showed a tendency towards higher composite LSR scores compared to treatment on 25 cm$^2$. The LSRs were still largely resolved after 2 weeks. Also, a higher proportion of subjects reported application site burning or similar symptoms (mainly mild or moderate) compared to treatment on 25 cm$^2$.

The present trial (LP0105-1020) investigated the 2-day MTD from the Trial LP0105-1012 (0.06%) and aimed at establishing the optimum treatment duration of this concentration on the trunk (except chest) and extremities. A more aggressive treatment regimen was considered needed for the skin of trunk (except chest) and extremities than the sensitive skin of face. Therefore, 1 or 2 extra treatment days was added to reach the limit of tolerability for these areas based on clinical experience obtained from Trial LP0105-1012 and phase 1/2b field treatment & dose-selection trials with Picato® (in Trial PEP005-006, PEP005-007, and PEP005-015). To evaluate the safety of this regimen, 2 safety interim analyses were conducted during the trial by a Data Monitoring Committee (DMC) that could recommend treatment groups to be discontinued if the pre-defined stopping criteria were met.
4 Trial Objectives

4.1 Primary Objective
To evaluate efficacy of ingenol mebutate gel 0.06% after once daily treatment for 2, 3 or 4 consecutive days compared to vehicle gel.

4.2 Secondary Objective
To evaluate the safety of ingenol mebutate gel 0.06% after once daily treatment for 2, 3, or 4 consecutive days compared to vehicle gel.
5 Investigational Plan

This was a randomised, double-blind, parallel groups, vehicle controlled, 8-week phase 2 trial conducted in the US and Australia.

5.1 Overall Trial Design

5.1.1 Overview of the Trial

Eligible subjects for inclusion in this trial had 5 to 20 clinically typical, visible, and discrete AKs on the trunk (except chest) or extremities within a contiguous area of approximately $250 \text{ cm}^2$ of sun-damaged skin.

Subjects attended a Screening Visit where they were assessed for eligibility and washout of concomitant medication, if applicable. This visit was to take place no more than 14 days prior to the first treatment visit at Day 1.

Eligible subjects were randomised into 4 different treatment groups; 3 active treatment groups and 1 vehicle group. Each group was planned for 60 subjects with 240 subjects randomised in total for the trial.

Subjects were randomised to application of ingenol mebutate gel 0.06%, vehicle gel, or a combination thereof. All subjects were to apply the investigational products for 4 days and the 3 active treatment groups were to apply ingenol mebutate gel for 2, 3, or 4 days, as follows:

- 4 days ingenol mebutate gel 0.06%
- 1 day vehicle gel, 3 days ingenol mebutate gel 0.06%
- 2 days vehicle gel, 2 days ingenol mebutate gel 0.06%
- 4 days vehicle gel

Please refer to a schematic overview in Figure 1 below. Subjects were followed for 8 weeks following the first application of investigational product.
5.1.2 Trial Periods

The trial consisted of 3 periods (screening period, treatment period, and observation period) which are briefly described below.

Screening Period (≤14 days prior to Day 1)

At Screening (Visit 1) subjects underwent the procedure for informed consent, and the subject’s eligibility was checked according to the inclusion/exclusion criteria. The following assessments were performed:

- Date of birth, sex, race, ethnic origin (self-report), height, weight, vital signs, Fitzpatrick skin type, relevant medical/surgical history, skin diseases, concurrent diagnoses, concomitant medication, and AK treatment history
- Abbreviated physical examination including general appearance, regional lymph nodes and dermatologic examination of the skin in general
- Vital signs (resting blood pressure and heart rate) and oral or ear temperature
- Safety blood sampling, including haematology- and biochemistry tests
- 5-20 clinically typical, visible and discrete AK lesions located on the trunk (except chest) or extremities within a contiguous area of approximately 250 cm² of sun-damaged skin.
The treatment area (arm with or without back of hand, trunk [except chest] or leg) was identified by the dermatologist and documented on a study transparency using a three-point landmark technique (Appendix 1.1, Appendix I).

Female subjects of childbearing potential had a urine pregnancy test.

**Treatment Period (Visit 2 (Day 1) to Visit 3 (Day 5))**

At Visit 2 (Day 1) subject eligibility was checked according to the inclusion and exclusion criteria. Once eligibility was confirmed, the subject was randomised into one of the 4 treatment groups.

The following assessments were re-confirmed:

- Medical/surgical history, concurrent diagnosis, skin diseases, and AK treatment history

The following assessments were performed:

- Concomitant medications, treatments, and procedures
- Clinical assessment of the treatment area, including LSRs and AK lesion count
- Abbreviated physical examination and vital signs
- ECG
- Application of investigational product
- Photo-damage in the treatment area
- Reporting of (S)AEs

A diary was handed out to the subjects to record burning sensation onset and duration to be completed on Day 1 to Day 4. The first dose of investigational product was applied under the supervision of the trial staff. The subject was to apply the subsequent doses at home and was therefore given the Subject Safety and Study Medication Instructions Sheet.

**Follow-up Period (Visit 3 (Day 5) to Visit 7 (Day 56±7 days))**

At Visit 3 (Day 5) the following assessments were performed:

- Reporting of concomitant medication, treatments, and procedures
- Safety blood sampling
- ECG
• Dermatologic examination of the treatment area including LSRs
• Reporting of (S)AEs
• Return of trial medication and study medication compliance

At Visit 4 (Day 10±2 days), Visit 5 (Day 17±2 days), and Visit 6 (Day 31±4 days) the following assessments were performed:
• Reporting of concomitant medication, treatments and procedures
• Reporting of LSRs
• Reporting of (S)AEs

In addition, at Visit 4 ECG was to be checked if abnormal at Visit 3 and at Visit 6 AK lesion count was performed.

At Visit 7 (Day 56±7 days) the following assessments were performed:
• Reporting of concomitant medication, treatments, and procedures
• Abbreviated physical examination and vital signs
• Dermatologic examination of the treatment area including LSRs and AK count
• Reporting of (S)AEs
• Treatment Satisfaction Questionnaire for Medication (TSQM)
• Photo-damage in the treatment area and global photo-damage outcome in the treatment area from baseline to Visit 7
• Cosmetic outcome (self-assessment)

Female subjects of childbearing potential had a urine pregnancy test.

**Unscheduled Visit/Early Termination**

If a subject was required to be seen due to a severe reaction, suspected pregnancy or an unresolved treatment-related AE or LSR, as deemed clinically significant by the investigator, an unscheduled visit could be performed. Only assessments that required follow-up were to be conducted if the subject was continuing in the trial. For early termination, all trial assessments scheduled were to be performed if possible.
Safety Interim Analyses

The methodology for the safety interim analyses is described in detail in the clinical study protocol, Appendix 1.1, Section 10.10.

Two safety interim analyses were conducted:

- The initial safety interim analysis were to be conducted when 12 subjects had been randomised in each treatment group and had been followed for 17 days
- The final safety interim analysis were to be conducted when 23 subjects had been randomised in each treatment group and had been followed for 17 days

The Data Monitoring Committee (DMC) conducted the 2 safety interim analyses (initial and final), analysing the number of Limiting Events which was either a Dose Limiting Toxicity (DLT) or other Limiting Events as detailed in the clinical study protocol, Appendix 1.1, Section 10.10.1. Please see Appendix 1.4 for a list of DMC members.

Prior to each safety interim analysis the DMC was provided blinded data for subjects with suspected limiting events. Based on this data the DMC assessed which subjects should be considered as having other limiting events. The safety interim analyses were then performed on unblinded data for the DMC to determine the Total Limiting Events in each trial group and compare with the pre-defined stopping criteria. The unblinded data was not available to the sponsor, trial site staff or the subjects during the trial and the sponsor did not access meeting minutes from closed DMC sessions during the trial. Stopping criteria for separate study groups or the entire trial for defined Total Limiting Events levels are detailed in the clinical study protocol, Appendix 1.1, Section 10.10.2 and 10.10.3. The outcome of the safety interim analyses are summarised in Section 5.8.

5.2 Discussion of Trial Design, Including the Choice of Control Groups

The entire clinical study protocol is presented in Appendix 1.1 and the unique pages of the case report form (CRF) are presented in Appendix 1.2.

The trial was designed as a phase 2, randomised, multi-centre, double-blind, vehicle-controlled, 8-week trial and the treatment period of 8 weeks was the same as Trial LP0105-1012 assessing ingenol mebutate gel treatment on full face, full balding scalp, or approximately 250 cm$^2$ on the chest.

The inclusion criteria and exclusion criteria followed the same design as previous clinical trials with ingenol mebutate gel. The exclusion criteria allowed for previous treatment for AK
and stipulated restrictions for prohibited treatments and procedures in defined time periods prior to the trial that could interfere with treatment with the investigational product.

An experienced dermatologist identified the treatment area and performed the dermatologic assessments of the treatment area. Preferably, the same dermatologist performed all dermatologic examinations for each individual subject to ensure standardisation of sequential assessments. The treatment area was larger than in previous clinical trials and therefore MTDs for ingenol mebutate gel was evaluated in the preceding Trial LP0105-1012, following 2 or 3 days of application to the full face, full balding scalp or approximately 250 cm$^2$ on the chest. In the Phase 3 programme with Picato® , LSR scores for the chest area were relatively high, and it therefore seemed that the chest area would be better grouped with the face. Part 2 of Trial LP0105-1012 therefore included subjects with AK on the chest in addition to subjects with AK on the face and scalp, and the present trial included AK on the trunk (except chest) and extremities.

The safety profile for the highest dose (0.06%) was similar to the safety profile known for Picato® where an area of 25 cm$^2$ is treated and this dose was therefore used in the present clinical trial. Apart from the 2- and 3-day trial design used in Trial LP0105-1012 a 4-day treatment group was included in the present trial, as a more aggressive treatment regimen was considered needed for the skin of trunk (except chest) and extremities than the sensitive skin of face. Addition of 1 or 2 extra treatment days was expected to reach the limit of tolerability for the trunk (except chest) and extremities based on clinical experience obtained from LP0105-1012 trial and phase 1/2b field treatment & dose-selection trials with Picato® (in Trials PEP005-006, PEP005-007, and PEP005-015). To evaluate the safety of this regimen, 2 safety interim analyses were conducted during the trial by a DMC that could recommend treatment groups to be discontinued if the pre-defined stopping criteria were met.

For efficacy, AK lesion count was recorded and complete AK clearance, partial AK clearance and percent reduction in number of AKs were estimated. The subject treatment satisfaction questionnaire (TSQM, Quintiles Inc.) was offered in Australian and UK English, American English, and universal Spanish to ensure that the subjects understood the questions.

For safety, AEs and LSRs were recorded. LSRs were graded using the same scale that was developed by the sponsor and used in the previous clinical studies. This is a defined grading scale to ensure that a clear and systematic assessment of LSRs is performed. The LSR grading scale employs a 0 to 4 scoring system for each category to be assessed with photographs and definitions of each grade.
5.3 Selection of Trial Population

5.3.1 Inclusion Criteria

1. Signed informed consent has been obtained

2. Subjects with 5 to 20 clinically typical, visible and discrete AKs within a contiguous area of approximately 250 cm² sun-damaged skin on either trunk (except chest), or extremities

3. Subjects at least 18 years of age

4. Female subjects must be either:
   - Non-childbearing potential, i.e., post-menopausal or have a confirmed clinical history of sterility (e.g., the subject is without a uterus) or,
   - Childbearing potential, provided there is a confirmed negative urine pregnancy test prior to trial treatment, to rule out pregnancy

5. Female subjects of childbearing potential¹ must be willing to use effective contraception from Visit 1 until the end of trial (Visit 7/Week 8)

6. Effective contraception is defined as follows:
   - Oral/implant/injectable/transdermal/oestrogenic vaginal ring contraceptives, intrauterine device, condom with spermicide, diaphragm with spermicide
   - Abstinence or partner’s vasectomy are acceptable if the female agrees to implement one of the other acceptable methods of birth control if her partner changes

¹ Female subjects are considered of childbearing potential unless they have had a hysterectomy or have undergone tubal ligation or have been post-menopausal at least one year prior to first visit.

5.3.2 Exclusion Criteria

1. Location of the treatment area (trunk (except chest) or extremities)
   - within 5 cm of an incompletely healed wound,
   - within 5 cm of a suspected basal cell carcinoma (BCC) or squamous cell carcinoma (SCC)
2. Prior treatment with ingenol mebutate within the selected treatment area (please refer to Prohibited Therapies and/or Medications: within 4 weeks prior to Visit 2/Day 1, no. 20)

3. Lesions in the treatment area that have:
   • atypical clinical appearance (e.g., hypertrophic, hyperkeratotic or cutaneous horns) and/or,
   • recalcitrant disease (e.g., did not respond to cryotherapy on two previous occasions)

4. History or evidence of skin conditions within the selected treatment area other than the trial indication that would interfere with the evaluation of the trial medication (e.g., eczema, unstable psoriasis, xeroderma pigmentosum)

5. Use of cosmetic or therapeutic products and procedures which could interfere with the assessments of the treatment areas

6. Clinical diagnosis/history or evidence of any medical condition (including clinically significant abnormal laboratory tests) that would expose a subject to an undue risk of a significant AE or interfere with assessments of safety and efficacy during the course of the trial, as determined by the investigator’s clinical judgment

7. Anticipated need for hospitalisation or out-patient surgery during the first 17 days after the first trial medication application. Note that cosmetic/therapeutic procedures are not excluded if they fall outside of the criteria detailed in Prohibited Therapies or Medications (see Exclusion Criteria Nos. 14 to 21).

8. Known sensitivity or allergy to any of the ingredients in ingenol mebutate gel

9. Presence of acute sunburn within the treatment areas

10. Participation in an investigational clinical trial within 30 days of entry into this trial

11. Subjects previously randomised in the trial

12. Female subjects who are breastfeeding

13. In the opinion of the investigator, the subject is unlikely to comply with the Clinical Study Protocol (e.g., alcoholism, drug dependency or psychotic state)

**Prohibited Therapies and/or Medications within 2 weeks prior to Visit 2/Day 1:**

14. Cosmetic or therapeutic procedures (e.g., use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing): within 2 cm of the treatment area
15. Use of topical keratolytic therapeutic products (e.g., alpha- and beta-hydroxy acids, including glycolic acid, lactic acid and other fruit acids, salicylic acid, topical retinoids, urea or light chemical peels): within 2 cm of the treatment area

16. Use of topical medicated creams, ointments, lotions, gels, foams or sprays including topical steroids: within 2 cm of the treatment area; artificial tanners: within 5 cm of the treatment area. (Non-medicated/non-irritant lotions/creams/sunscreens are acceptable)

Prohibited Therapies and/or Medications: within 4 weeks prior to Visit 2/Day 1:

17. Treatment with immunomodulators (e.g., azathioprine), cytotoxic drugs (e.g., cyclophosphamide, vinblastine, chlorambucil, methotrexate, podophyllin, camptothecin) or interferon/interferon inducers

18. Treatment with systemic medications that suppress the immune system (e.g., cyclosporine, prednisone, methotrexate)

19. Treatment/therapy with ultraviolet light A (UVA) or ultraviolet light B (UVB).

20. Treatment with 5-fluorouracil (5-FU), imiquimod, ingenol mebutate, topical diclofenac sodium, or photodynamic therapy (please refer to exclusion criterion no. 2)

Prohibited Therapies and/or Medications within 6 months prior to Visit 2/Day 1:

21. Use of systemic retinoids (e.g., isotretinoin, acitretin, bexarotene) or biologic/monoclonal antibody therapies (e.g., alefacept, infliximab, rituximab)

5.3.3 Removal of Subjects from Therapy or Assessment

Subjects could withdraw for any of the following reasons:

1. Unacceptable treatment efficacy: the investigator was free to withdraw the subject at any time for medical reasons.

2. Unacceptable adverse events or LSRs: any adverse event or LSR that the investigator or the subject considered unacceptable.

3. Exclusion criteria: any exclusion criterion which emerged/became apparent during the subject’s participation in the clinical trial.

4. Voluntary withdrawal: subjects were free to withdraw from the clinical trial at any time and for any reason.

5. Other reasons: other reasons than those stated above which required the subject to (be) with-draw(n) were to be specified.
Subjects who were discovered, after enrolment/randomisation, not to have fulfilled all inclusion/exclusion criteria at time of enrolment, were to be withdrawn from treatment unless the investigator, based on clinical and ethical evaluation, found withdrawal from treatment inappropriate. The final efficacy assessment (at the correct scheduled time) should, however, be attempted to be completed for all subjects. Such deviation(s) from the clinical study protocol were to be reported to LEO (and HREC/IRB, as appropriate) and recorded in the clinical study report.

Subjects who withdrew from treatment for any other reasons were likewise, as a minimum, to be asked to complete the final efficacy assessment (at the correct scheduled time).

Reason(s) for withdrawal were to be recorded in the CRF and withdrawn subjects were not replaced.

5.4 Treatments

5.4.1 Treatments Administered

Ingenol mebutate gel, 0.06%, and vehicle gel were to be applied topically to a contiguous area of approximately 250 cm² sun-damaged skin on trunk (except chest), or extremities. The investigational products were to be applied by the subject under supervision by the site staff at first treatment and by the subject alone at the second, third, and fourth treatment following the guidelines in Sections 10.6.4 and 10.6.5 in the clinical study protocol (Appendix 1.1).

5.4.2 Investigational Products

Details of the investigational product and comparator product are given in Table 1 and Table 2.
### Table 1  Identity of investigational product

<table>
<thead>
<tr>
<th>Finished product name investigational product:</th>
<th>Ingenol mebutate gel, 0.06%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation:</td>
<td>Gel</td>
</tr>
<tr>
<td>Active ingredient name/strength:</td>
<td>Ingenol mebutate 0.06 w/w</td>
</tr>
<tr>
<td>Excipients:</td>
<td></td>
</tr>
<tr>
<td>Manufacturer’s name:</td>
<td>LEO Pharma A/S</td>
</tr>
<tr>
<td>Batch number/expiry date</td>
<td>132607101/Aug-2015</td>
</tr>
</tbody>
</table>

### Table 2  Identity of comparator product

<table>
<thead>
<tr>
<th>Finished product name:</th>
<th>Vehicle gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation:</td>
<td>Gel</td>
</tr>
<tr>
<td>Active ingredient name/strength:</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Excipients:</td>
<td></td>
</tr>
<tr>
<td>Manufacturer’s name:</td>
<td>LEO Pharma A/S</td>
</tr>
<tr>
<td>Batch number/expiry date:</td>
<td>131357101/Apr-2015</td>
</tr>
</tbody>
</table>

At the trial sites the investigational products were stored in a refrigerator $\text{°F} (\text{°C})$ in a secure and restricted access area, with refrigerator temperature monitored and recorded continuously. Following dispensing for application at home, subjects were to place the tubes in the home refrigerator as soon as possible. The tubes should be refrigerated and:

- stored sufficiently segregated from foodstuffs to avoid exposure to the trial medication
- stored safely to ensure against inadvertent exposure to non-participants (including children and pets)
For details on labelling and storage of the investigational product, see Sections 10.6.1 and 10.6.2 of the clinical study protocol (Appendix 1.1).

5.4.3 Method of Assigning Subjects to Treatment Groups

Subjects who were found to comply with all the inclusion and exclusion criteria were randomised to receive treatment with either ingenol mebutate gel, vehicle gel, or a combination thereof. Treatment assignment was pre-planned according to a computer generated blocked randomisation schedule in a 1:1:1:1 ratio stratified per trial site. Treatment group assignment was generated through an IWR system.

5.4.4 Selection and Timing of Dose for each Subject

The selection of dose of the investigational product was based on the dose escalation clinical trial (Trial LP0105-1012) assessing safety of ingenol mebutate gel applied on full face, full balding scalp, or approximately 250 cm$^2$ on the chest.

There were no specific requirements for timing of dose or time of dosing to dietary intake.

5.4.5 Blinding

The clinical trial was double blinded, i.e. the sponsor, trial site staff, and the subject were blinded to the assigned treatment group.

The packaging and labeling of the investigational products contained no evidence of their identity. It was not considered possible to differentiate between the investigational products solely by sensory evaluation. Consequently, it was expected that the subjects and the site staff were to remain unaware of the individual treatment assignment during the conduct of the clinical trial.

For blinding procedure at the safety interim analyses, please see ‘Safety Interim Analyses’, Section 5.1.2.

5.4.6 Prior and Concomitant Therapy

Prior to the Trial

Prohibited treatments and procedures prior to trial entry are detailed in the exclusion criteria, see Section 5.3.2 for details.
During the Trial
Use of non-marketed or other investigational products during the trial was not permitted.

All medications currently being taken at the time of Visit 1 were to be recorded in the CRF, along with the reasons for administration of the medication or treatment as well as location, described as the treatment area, outside the treatment area or not applicable.

Any medication, treatments and procedures during the trial were to be recorded along with the indication.

Subjects could be advised to use icepacks and analgesics to attenuate burning sensation and pain. Icepacks were not considered a medical intervention but were to be recorded as a concomitant treatment.

Subjects were not to undergo any elective medical procedure without prior consultation with the investigator. Elective procedures (e.g., minor day-surgery, dental surgery, etc.) that required hospitalisation or anaesthesia were to be deferred during the first 17 days after first application (Visit 2), whenever clinically appropriate or possible.

Prohibited treatments and procedures during the trial are given in Table 3 below.
<table>
<thead>
<tr>
<th>Prohibited treatment/procedure</th>
<th>Location/action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosmetic or therapeutic procedures (e.g., use of liquid nitrogen, surgical excision, curettage,</td>
<td>Within 5 cm of the treatment area</td>
</tr>
<tr>
<td>dermabrasion, medium or greater depth chemical peel, laser resurfacing)</td>
<td></td>
</tr>
<tr>
<td>Use of topical keratolytic therapeutic products (e.g., alpha- and beta- hydroxy acids,</td>
<td>Within 5 cm of the treatment area</td>
</tr>
<tr>
<td>including glycolic acid, lactic acid and other fruit acids, salicylic acid, topical retinoids,</td>
<td></td>
</tr>
<tr>
<td>urea or light chemical peels)</td>
<td></td>
</tr>
<tr>
<td>Topical medicated creams, ointments, lotions, gels, foams or sprays, including topical steroids,</td>
<td>Within 5 cm of the treatment area until Visit 5</td>
</tr>
<tr>
<td>Non-medicated/non-irritant salves/emollients</td>
<td>During treatment days</td>
</tr>
<tr>
<td>Subjects should wash treatment area with mild soap before using salves/emollients</td>
<td></td>
</tr>
<tr>
<td>Make-up</td>
<td>On the treatment area until Visit 5</td>
</tr>
<tr>
<td>Any topical medications or treatments that might influence the intended effects or mask the</td>
<td>Within 5 cm of the treatment area until Visit 5</td>
</tr>
<tr>
<td>side effects of treatment, such as topical corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Artificial tanners</td>
<td>Within 5 cm of the treatment area</td>
</tr>
<tr>
<td>Treatment/therapy with UVA or UVB</td>
<td>Anywhere</td>
</tr>
<tr>
<td>Excessive or prolonged exposure to ultraviolet light (e.g., sunlight, tanning beds)</td>
<td>Anywhere</td>
</tr>
<tr>
<td>5-FU, imiquimod, ingenol mebutate, topical diclofenac or photodynamic therapy</td>
<td>Anywhere</td>
</tr>
<tr>
<td>Immuno-modulators (e.g., azathioprine), cytotoxic drugs (e.g., cyclophosphamide, vinblastine,</td>
<td>Excluded</td>
</tr>
<tr>
<td>chlorambucil, methotrexate, podophyllin, camptothecin) or interferon/interferon inducers</td>
<td></td>
</tr>
<tr>
<td>Medications that suppress the immune system (e.g., cyclosporine, prednisone, methotrexate)</td>
<td>Excluded</td>
</tr>
<tr>
<td>Systemic retinoids (e.g., isotretinoin, acitretin, bexarotene) or biologic/monoclonal antibody therapies (e.g., alefacept, infliximab, rituximab)</td>
<td>Excluded</td>
</tr>
<tr>
<td>Other investigational drugs, agents or devices or any chemotherapy for cancer treatment or any medications or treatments that might influence the intended effects or mask the side effects of trial medication.</td>
<td>Excluded</td>
</tr>
<tr>
<td>Elective surgical procedures.</td>
<td>Note: may take place with discretion following Visit 5</td>
</tr>
</tbody>
</table>

### 5.4.7 Treatment Compliance

The investigator was fully responsible for the investigational products at the trial site but could delegate dispensing of the investigational product, e.g., to a hospital pharmacy as locally applicable. The person responsible for dispensing the investigational products was responsible for maintaining adequate control of the investigational products and for documenting all transactions with them. The investigational products were to be stored in a safe and secure place, and proper dispensing arrangements were to be made.

**Sponsor-Investigator-Subject Drug Accountability**

All investigational products supplied by the contract manufacturing organisation (CMO) were to be returned to the CMO shortly after enrolment was completed, once investigational product accountability was verified for all subjects at the trial site. Prior to their return, site as well as individual subject drug accountability was to be fully accounted for by the monitor with the help of the person responsible for dispensing the investigational products. Accountability was documented by using drug accountability forms including information of number of used/unused tubes per kit.

When enrolment in the trial was completed and the subjects had returned investigational products to the site, the monitor performed drug accountability for all trial medication at the site and assisted in the return to the CMO.

The end of trial drug accountability was performed as outlined in the clinical study protocol (Appendix 1.1).
Treatment Compliance
At Visit 3, the subject was asked if she/he had used the medication as prescribed. If this was not the case, the degree and nature of non-compliance was to be specified.

5.5 Assessments

5.5.1 Frequency and Timing of Measurements
The schedule of all trial procedures for all trial visits is presented in Table 4.


### Table 4  Schedule of trial procedures

<table>
<thead>
<tr>
<th>Visit (window)</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>Visit 6</th>
<th>Visit 7</th>
<th>Unscheduled(^1) / Early Term.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>In-/exclusion criteria</td>
<td>X</td>
<td>X(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics: race, ethnicity, sex, date of birth</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height &amp; Weight</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick skin type</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical / Surgical history</td>
<td>X</td>
<td>X(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medication, treatments, procedures</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Skin diseases</td>
<td>X</td>
<td>X(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AK treatment history</td>
<td>X</td>
<td>X(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Physical examination</td>
<td>X</td>
<td>X</td>
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<td></td>
<td>X</td>
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<tr>
<td>Vital signs</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Safety blood sampling(^3)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-lead ECG</td>
<td>X</td>
<td>X</td>
<td>X(^4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine pregnancy test(^5)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identify treatment area</td>
<td>X</td>
<td>X(^2)</td>
<td></td>
<td></td>
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<tr>
<td>AK assessment</td>
<td>X</td>
<td>X</td>
<td></td>
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<td>X</td>
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<tr>
<td>Randomisation</td>
<td>X</td>
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<tr>
<td>LSR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Apply trial medication(^6)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Compliance with treatment</td>
<td>X</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Return of trial medication</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>TSQM</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Burning sensation diary(^7)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Photo-damage assessment by Investigator</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Global photo-damage outcome assessment by Investigator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Cosmetic outcome assessment by Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) Only assessments that required follow-up were to be conducted;  \(^2\) Re-check;  \(^3\) To be repeated at visits 4-7 until recovered for parameters outside the reference range;  \(^4\) To be performed only if abnormal at Visit 3;  \(^5\) Only subjects of childbearing potential;  \(^6\) The first treatment were to be applied at Visit 2 under supervision of trial staff. Subsequent treatments were to be applied by the subject at home;  \(^7\) To be completed by the subject Day 1 to Day 4
5.5.2 Baseline Characteristics and Demographics Assessed

At Visit 1 the subjects’ demographic details (date of birth, sex, race, ethnic origin, height, weight, Fitzpatrick skin type) were recorded. Subjects self-reported their ethnicity (Hispanic or Latino, not Hispanic or Latino) and race (American Indian or Alaska Native; Asian, Black or African American; Native Hawaiian or Other Pacific Islander; White, Other). Skin type was assessed by the investigator using the Fitzpatrick Skin Types:

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Always burns easily, never tans</td>
</tr>
<tr>
<td>II</td>
<td>Always burns easily, tans minimally</td>
</tr>
<tr>
<td>III</td>
<td>Burns moderately, tans gradually (light brown)</td>
</tr>
<tr>
<td>IV</td>
<td>Burns minimally, always tans well (moderate brown)</td>
</tr>
<tr>
<td>V</td>
<td>Rarely burns, tans very well (moderate brown)</td>
</tr>
<tr>
<td>VI</td>
<td>Never burns, deeply pigmented</td>
</tr>
</tbody>
</table>

Relevant medical/surgical history, concurrent diagnosis, skin diseases, AK treatment history, concomitant medication, treatments and procedures were also recorded. In addition, laboratory biochemistry and haematology tests were performed, vital signs were obtained, an abbreviated physical examination was performed, and a standard 12-lead ECG was recorded as indicated in Table 4.

5.5.2.1 Investigator’s Assessments

Identification of the treatment areas and dermatologic assessments of the treatment areas were performed by a board-certified dermatologist or equivalent. The same dermatologist was to attempt to perform all dermatologic examinations of each individual subject.

The (sub)investigator made the following clinical assessments:

Identification of the Treatment Area

At Visit 1 identification of the treatment area was to be documented on a study transparency using a three-point landmark technique. The identification of the treatment area was confirmed at Visit 2.

At all subsequent visits, the transparency were to be used to re-locate the treatment area for assessment of the treated skin on the trunk or extremities.
Local Skin Responses
Assessment of LSRs in the treatment area was to be performed at Visit 2 as indicated in Table 4.

AK Lesion Count
The number of clinically visible AK lesions identified in the treatment area was to be recorded at Visit 1 as indicated in Table 4.

Photo-Damage Assessment
A clinical (visual and tactile) assessment of the extent of photo-damage in the treatment area was made at Baseline with respect to fine wrinkling, coarse wrinkling, mottled pigmentation, roughness, sallowness, skin laxity, and telangiectasia.

5.5.2.2 Subject’s Assessment
At Baseline the subjects were asked to complete a Burning Sensation Diary starting at Day 1. Please see Section 5.5.4.4 for details.

5.5.3 Efficacy Measurements Assessed

5.5.3.1 Investigator’s Assessment of AK Lesion Count
The clinical assessment of AK lesion count was performed by an experienced dermatologist. The same dermatologist was to attempt to perform all investigator’s assessments of AK lesion count of each individual subject. The number of clinically visible AK lesions identified in the treatment area was recorded at Visit 1 and for the area treated at the visits specified in Table 4.

The location of the treatment area was to be recorded in the CRF at Baseline using the following categories: arm including back of hand, arm not including back of hand, leg, or trunk.

The AK lesion count was to be done separately for AKs on back of hand and AKs located on other areas than back of hand. At Baseline the total number of AK lesions was to be between 5 and 20 in the entire treatment area.

5.5.3.2 Investigator’s Assessment of Photo-Damage

Photo-Damage Assessment
At Baseline and Week 8 the Investigator made a clinical (visual and tactile) assessment of the extent of photo-damage in the treatment area with respect to fine wrinkling, coarse wrinkling, mottled pigmentation, roughness, sallowness, skin laxity, and telangiectasia.
Severity was assessed on a 5-point scale: none (0), mild (1), moderate (2), severe (3), and extreme (4).

**Global Photo-damage Outcome Assessment**
At Week 8 the Investigator made an overall clinical (visual and tactile) assessment of the subject’s photo-damage change from Baseline in the treatment area including an integrated assessment of fine wrinkling, coarse wrinkling, mottled pigmentation, roughness, sallowness, skin laxity, and telangiectasia based on the subject’s appearance at the baseline visit.

The scoring was on a 7-point symmetric scale: marked improvement (+3), moderate improvement (+2), minor improvement (+1), no change (0), minor worsening (-1), moderate worsening (-2), and marked worsening (-3).

5.5.3.3 Subject’s Assessments

**Treatment Satisfaction Questionnaire for Medication**
The subjects were to complete Treatment Satisfaction Questionnaire for Medication (TSQM) as specified in Table 4. This was to be done when the subject arrived at the clinic before any other assessments were completed for the subject.

**Cosmetic Outcome Assessment**
At Week 8 the subjects were to complete a self-assessment questionnaire evaluating the change in the 1) overall appearance of the skin and 2) overall feel of the skin after treatment.

The scoring was on a 4-point scale: worsened, no change, somewhat improved, and much improved. Please refer to Appendix 1.1, Appendix III.

5.5.4 Safety Measurements Assessed

5.5.4.1 Adverse Events

**Definition of an Adverse Event**
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH GCP, E6 (R1)).

**Definition of a Serious Adverse Event**
A serious adverse event (SAE) is any untoward medical occurrence that
• results in death
• is life-threatening
• requires inpatient hospitalisation or prolongation of existing hospitalisation
• results in persistent or significant disability/incapacity
• is a congenital anomaly/birth defect

or

• other medically important conditions* including SCC and BCC in the treatment area.

* Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are allergic bronchospasm, blood dyscrasias and convulsions.

**Recording of Adverse Events**
Global Pharmacovigilance, LEO was responsible for the assessment of expectedness according to LEO procedures. The relevant reference document for this clinical trial was Investigator’s Brochure, edition 3 and subsequent updates.

At all visits, the subject was asked a non-leading question by the investigator: “How have you felt since I saw you last?” No specific symptoms were asked for. The investigator was also to observe the subject for any changes not reported by the subject and record these changes.

Any medical changes until Visit 2 was to be included in the medical history and not reported as an AE.

If there were no AEs to record, no further questions was asked and “NO” was stated. In case there were one or more AEs to record, “YES” was stated and the investigator recorded the event term, intensity, duration, suspected causal relationship to the investigational product and outcome.

Only medically qualified personnel assessed AEs. A board-certified dermatologist or equivalent was to do all dermatologic examinations, LSR- and AE- evaluations of the treatment area.

For AEs recorded on the day of first trial treatment, it was to be specified whether the AE started prior to or after first application of medication.
Local Skin Responses which matched the criteria in the LSR Grading Scale were to be reported as LSRs in the CRF and not as AEs even if they required treatment.

Any treatment was to be recorded on the concomitant medication page of the CRF together with the most important LSR (e.g., swelling should be reported as swelling-LSR). Any skin responses identified in the treatment area which did not match the criteria in the LSR Grading Scale were to be reported as AEs.

**Reporting of Adverse Events**

Events reported by the subject or observed by the (sub)investigator and that fell into any of the above definitions were to be recorded on the AE page of the CRF and described in the following manner:

The **nature** of the event were to be described in precise English medical terminology (i.e., not necessarily the exact words used by the subject). Whenever possible, a specific diagnosis was to be stated (e.g., allergic contact dermatitis).

For AEs the location was to be part of the AE description and to be described as ‘in the treatment area’, ‘outside the treatment area’ or ‘not applicable’.

The **intensity** of the event was to be described in terms of mild, moderate or severe according to the investigator’s clinical judgement.

- **Mild**: The AE does not interfere in a significant manner with the subject’s normal functioning level and requires no medical intervention.
- **Moderate**: The AE interferes with the subject’s normal functioning level and may or may not require medical intervention.
- **Severe**: The AE produces significant impairment of the subject’s functioning or requires medical intervention.

The **duration** of the event was to be reported as the start date and stop date of the event.

The causal relation of the event to the use of the investigational product was to be described in terms of probable, possible, not related or not assessable according to the following:

**Probably Related**

- Follows a reasonable temporal sequence from the administration of the investigational product
- Could not be reasonably explained by the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject
- Follows a known pattern of response to the investigational product
- Disappears or decreases on cessation or reduction in dose of the investigational product
- Re-appears or worsens upon re-challenge

**Possibly Related**

- Follows a reasonable temporal sequence from the administration of the investigational product
- Could also be reasonably explained by the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject
- Follows a known pattern of response to the investigational product

**Not Related**

- Does not follow a reasonable temporal sequence from administration of the investigational product
- Is better explained by other factors like the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject
- Does not follow a known pattern of response to the investigational product

**Not Assessable**

- The adverse event cannot yet be judged otherwise because present information is insufficient or contradictory. A final assessment (i.e., probably, possibly or not related) shall be made as more information becomes available, at the latest when the subject has completed the trial.
The outcome of the event was to be classified and handled as follows:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered/resolved</td>
<td>The event has stopped. The stop date of the event must be recorded.</td>
</tr>
<tr>
<td>Recovering/resolving</td>
<td>The subject is clearly recovering from an event. The event is, however, not yet completely resolved. Follow-up on the event is required until final outcome is established.</td>
</tr>
<tr>
<td>Not recovered/not resolved</td>
<td>Event is still ongoing. Follow-up on the event is required until final outcome is established.</td>
</tr>
<tr>
<td>Recovered with sequelae</td>
<td>The event has reached a state where no further changes are expected and the residual symptoms are assumed to persist. An example is hemiparesis after stroke. The stop date of the event must be recorded.</td>
</tr>
<tr>
<td>Fatal</td>
<td>The subject has died as a consequence of the event. Date of death is recorded as stop date for the adverse event.</td>
</tr>
<tr>
<td>Unknown</td>
<td>Unknown to investigator, e.g., subject lost to follow-up.</td>
</tr>
</tbody>
</table>

Once a subject had completed the clinical trial, all AEs and LSRs classified as possibly or probably related to the investigational product and deemed clinically significant were to be followed for 2 months or until final outcome was determined, whichever came first.

**Other Events to be Reported**

**Pregnancy**

Any pregnancy which occurred during the clinical trial with an investigational product was to be reported to LEO within 24 hours of first knowledge using the Pregnancy Follow-up Form. This also included female partners of male trial participants. All such pregnancies were to be followed up until delivery or termination and final outcome was reported.

**Overdose, Medication Errors, Misuse and Intended Abuse**

AEs originating from overdose, medication errors, misuse and intended abuse were to be documented on the AE form of the CRF book. In addition the term overdose/medication error/misuse/intended abuse was to be documented on a separate line.
Aggravation of Condition

Any clinically significant aggravation/exacerbation/worsening of the initially treated condition compared to baseline, judged by an overall medical assessment, was to be reported as an AE.

Serious Adverse Events

Reporting of Serious Adverse Events

Any SAE, related or unrelated to the investigational product or any trial procedure after signature of the Informed Consent Form, was to be reported to LEO Pharma on the (paper) Serious Adverse Event Form – Clinical Trial within 24 hours of first knowledge.

Note: Planned hospitalisation or planned prolonged hospitalisation did not fulfill the criteria for being an SAE. The elective nature of the event was to be clearly documented in the subject’s medical record.

SAEs were to be reported on the AE form of the CRF book. Additionally, reports were to be made using the (paper) Serious Adverse Event Form – Clinical Trial, supplied by LEO Pharma. Apart from the assessment of the intensity, causal relationship to the investigational product(s) and/or trial procedures, the action taken and the outcome to date, this report contained a comprehensive narrative description of the course of the event.

The completed Serious Adverse Event Form – Clinical Trial was to be faxed or scanned and e-mailed to Global Pharmacovigilance, LEO or the local LEO affiliate.

All other relevant reports of diagnostic procedures, hospital records, autopsy reports, etc. were to be included as applicable or upon request from Global Pharmacovigilance.

The IRBs/HRECs, regulatory authorities and concerned investigators were to be notified of SAEs according to the current regulation and local requirements.

All SUSARs were subject to expedited reporting to regulatory authorities, IRBs/HRECs and other committees, e.g., DMC. Global Pharmacovigilance un-blinded such cases prior to reporting. Investigators were to remain blinded. Please confer with the clinical study protocol, Appendix 1.1, Section 10.6.9.

SAEs were to be followed indefinitely until a final outcome had been established, i.e., the follow-up could continue beyond the end of the clinical trial.
SAEs occurring after the completion of the clinical trial (including any protocol required post-treatment follow-up period) were not routinely sought or collected. However, such events were to be reported to LEO if the investigator became aware of them.

5.5.4.2 Investigator’s Assessment of Local Skin Responses

The clinical assessment of LSRs was performed by an experienced dermatologist. The same dermatologist was to attempt to perform all investigator’s assessments of LSRs of each individual subject.

Assessment of LSRs in the treatment area was performed at Visit 2 and at all subsequent visits as indicated in schedule of trial procedures in Table 4.

LSRs were defined as erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. The presence/absence and grade of each LSR was recorded using the LSR grading scale (Appendix 1.1, Appendix II). This grading scale was also provided as a hard copy to the sites for ease of reference. Any LSRs identified within the treatment area which did not match the criteria in the LSR grading scale were to be reported as AEs.

5.5.4.3 12-lead ECG

A standard 12-lead ECG was to be recorded after 5 minutes of rest in the supine position. Each recording was marked with the subject number, date and time of the recording.

The following ECG parameters were to be recorded: heart rate, PR interval, QRS duration, QT interval, QTc interval. The ECG was to be performed at the visits specified in Table 4. If the ECG was abnormal and of clinical significance, it was up to the investigator’s discretion to enroll the subject into the trial. Clinically significant ECG findings from Visit 1 were to be recorded as medical history and clinically significant ECG findings from subsequent visits were to be recorded as AEs.

The ECG data was interpreted by a central CRO and the results were made available to the investigator.

5.5.4.4 Subject’s Assessment

Burning Sensation Diary

The subjects were asked to complete a Burning Sensation Diary recording onset and duration of burning as well as the subject's feeling of burning (using five descriptive categories). The diary was to be completed on days 1 to 4.
5.5.4.5 Vital Signs and Physical Examination

Vital signs (resting blood pressure and heart rate) and oral or ear temperature were obtained.

Abbreviated physical examination including general appearance, regional lymph nodes, and dermatological examination of the skin in general was conducted.

5.5.4.6 Clinical Laboratory Tests

Blood samples were collected for central laboratory analyses (haematology and biochemistry) at visits specified in Table 4.

Haematology
Leucocytes, erythrocytes, haemoglobin, haematocrit, thrombocytes, mean corpuscular volume, partial automated differentiation: lymphocytes, monocytes, eosinophils, basophils, neutrophils.

Biochemistry
Total bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST) / serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT) / serum glutamic pyruvate transaminase (SGPT), lactate dehydrogenase, creatinine, urea, uric acid, total protein, albumin, globulin, glucose, bicarbonate, inorganic phosphate, sodium, potassium, calcium, chloride, magnesium, high sensitivity C-reactive protein.

The sampling, storage and shipment procedures were to be carried out according to the central laboratory manual.

A minimum volume of blood, corresponding to approximately 10 mL, was taken for haematology and biochemistry panels.

For female subjects of childbearing potential a urine pregnancy test (tested locally) was performed.

Laboratory kits containing all equipment required for laboratory analyses were provided by the central laboratory.

The investigator was to evaluate all results outside the reference range (‘clinically significant’ or ‘not clinically significant’) and sign and date the results form. The signed and dated version was filed with the investigator’s trial documentation. If a result was considered clinically significant and it fulfilled the criteria for a clinical laboratory AE, it was to be reported in accordance with Section 10.7.4 of the clinical study protocol (Appendix 1.1). Clinically
significant laboratory findings at Screening were to be recorded as ongoing medical history, and it was at the investigator’s discretion if the subject was to be enrolled into the trial.

5.5.5 Appropriateness of Measurements

Investigator Assessments

Efficacy

AK Lesion Count
To evaluate efficacy the investigator documented the location of the treatment area and the presence of AK lesions in the selected treatment area. The identification of the treatment area and documentation of AK lesions was conducted as in the previous studies with ingenol mebutate gel.

Photo-damage Assessment and Global Photo-damage Outcome Assessment
The photo-damage assessment monitored the extent of photo-damage in the treatment area with respect to severity along a 5-point scale of 7 skin characteristics. At Baseline and Week 8 the same investigator was to perform the assessment which was supportive to the global photo-damage outcome assessment.

The global photo-damage outcome assessment monitored the change in the photo-damage characteristics from Baseline to Week 8. It was an integrated assessment based on best clinical judgement of the overall skin changes along a 7-point scale with the photo-damage assessment result as support.

Both photo-damage assessments were developed by LEO.

Safety
To evaluate safety LSRs were assessed using a defined LSR rating scale and all AEs reported by the subject or observed by the investigator were recorded. These and other investigator safety assessments described in Section 5.5.4 have been used in previous trials with ingenol mebutate gel.

Subject Assessments

Efficacy

Treatment Satisfaction Questionnaire for Medication
The Treatment Satisfaction Questionnaire for Medication is a validated measure of treatment satisfaction for medication developed by Quintiles Inc.

Cosmetic Outcome
The cosmetic outcome is a questionnaire implemented by LEO that was handed out to the subject at the end of the trial. It captures the subject's own evaluation of appearance and feel of the skin after end of treatment.
Safety

Burning Sensation Diary

Due to a high proportion of subjects reporting a burning sensation in Part 1 of the Trial LP0105-1012 (preceding Trial LP0105-1020), LEO constructed a self-administered questionnaire, the Burning Sensation Diary, which was used in part 2 of Trial LP0105-1012 and in Trial LP0105-1020. The diary was completed by subjects on treatment days and was implemented to gain more knowledge on the subject’s own perception of the burning sensation, as well as the onset and duration of burning after application of ingenol mebutate. Entries of burning sensation in this diary resulted in an AE also being reported for the subject. It should be noted that the reported frequency of burning sensation is likely to be higher than it would be with spontaneous reporting.

5.6 Endpoints/Response Criteria

5.6.1 Primary Response Criterion

- Complete clearance of AKs at Week 8

5.6.2 Secondary Response Criteria

- Reduction in AK count from baseline to Week 8
- Partial clearance of AKs at Week 8, defined as at least 75% reduction from baseline in the number of clinically visible AKs

5.6.3 Evaluation of (Serious) Adverse Events & LSRs

- Incidence of AEs and SAEs
- Incidence and severity of LSRs following treatment
- Incidence of AEs and LSRs leading to discontinuation of trial medication

5.6.4 Evaluation of Laboratory Data

- Abnormal haematology and biochemistry laboratory values

5.6.5 Evaluation of Other Observations

- Change from baseline to Visit 3 in ECG assessments
- TSQM
- Burning sensation during treatment
- Investigator’s Global Photo-damage outcome at Week 8
Subject’s Cosmetic outcome score with regards to change in overall feel of skin of treatment area at Week 8

Subject’s Cosmetic outcome score with regards to change in overall appearance of treatment area at Week 8

5.7 Data Quality and Assurance

LEO has implemented a system of quality assurance, including all the elements described in this report. Within this system company Standard Operating Procedures (SOPs) are implemented to ensure that clinical trials are conducted in compliance with regulatory requirements and Good Clinical Practice (GCP). Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

Trial sites, facilities, laboratories and all data (including sources) and documentation were available for GCP audit by LEO or inspection by competent authorities.

Investigator meetings were conducted before the start of the trial in Australia and in the United States, including training in GCP and sponsor trial procedures, the electronic CRF system, and investigator assessments.

Two investigator site audits were performed during the trial to ensure that established procedures and the documentation generated were in accordance with GCP, applicable regulations and contracts. There were no critical non-conformities and the audit certificates verified that all findings as documented in the audit reports had been addressed (see Appendix 1.8).

Trial Monitoring

LEO, as sponsor of this clinical trial, is responsible to the authorities for assuring the proper conduct of the trial with regard to protocol adherence and validity of the data recorded on the CRFs. The company, therefore, assigned persons to monitor this clinical trial. It was their duty to serve as the principal link between (sub)investigators and LEO and advise the investigators on the collection and maintenance of complete, legible, well organised, and easily retrievable data for the clinical trial. In addition, they were to explain to the investigators any aspect of the (conduct of the) trial, including interpretation of the protocol, and purpose of collection of the specified data and reporting responsibilities.

Case Report Forms

In this clinical trial, data were collected by means of Remote Data Capture (RDC). The investigator, or staff authorised by the investigator, were to enter subject data into an electronic CRF designed by LEO. A uniquely numbered CRF book was used for each subject
enrolled. Data recorded in the electronic CRFs were accessible to site staff through a secure internet connection immediately after entry of data had taken place. The CRFs were to be maintained in an up-to-date condition at all times by the investigator.

Data Handling
Subject data were to be entered into the electronic CRF by authorised site staff in a timely manner. Data were to be entered by site staff and systematic data validation was performed through the discrepancy management system within the data collection software. Queries for discrepant data were generated either automatically by the system upon entry or generated manually by the monitor or the trial data manager. All queries, whether generated by the system or by a user, would be in an electronic format. This systematic validation was made to ensure that a clean and consistent database was provided prior to the statistical analysis being performed.

5.8 Changes to the Conduct of the Trial
The screening (but not randomisation) of subjects for the trial was paused for 10 days (25-Apr-2014 to 05-May-2014) due to a recommendation from the DMC. The reason was to account for the high recruitment rate which would have resulted in the vast majority of subjects being randomised and exposed before the completion of the final safety interim analysis.

Randomisation (but not screening) of subjects was paused 5-May-2014 to 14-May-2014 due to a delay in providing clean data to the DMC to proceed with the final safety interim analysis.

Two safety interim analyses were planned. No changes were made as a result of the first safety interim analysis.

The outcome of the final safety interim analysis was that the DMC found that the criterion for closing the treatment group where subjects received 4 days treatment with ingenol mebutate gel was met, as 10 limiting events (9 DLTs and 1 other limiting event) were observed in 23 patients. The DMC recommended the sponsor to close the 4-day active treatment group and the recommendation was endorsed by the sponsor.

Changes to the conduct of the planned protocol analyses are detailed in the statistical analysis plan update (SAPU) and changes to the SAPU are found in Section 6.3.
6 Statistical Methods

6.1 Determination of Sample Size

The null hypothesis is that there is no difference in efficacy between an active treatment group and the vehicle group. This hypothesis was tested against the alternative hypothesis that there is a difference. A total of 240 subjects were to be included, 60 subjects in each treatment group. With this sample size, a two group continuity corrected chi-square test will have 80% power to detect a difference in complete clearance rates between an active group and the vehicle group, assuming the true estimate is 28% in the active group and 7% in the vehicle group testing at a two-sided 5% significance level.

A single trial site should aim to recruit at least 8 subjects and not more than 24 (10% of the total sample size).

6.2 Statistical and Analytical Plan

The statistical analysis was planned in the clinical study protocol, Appendix 1.1, and further detailed in the statistical analysis plan update (SAPU), Appendix 1.9.

6.2.1 Subject Qualification for Analysis

All subjects for whom a signed informed consent was obtained and a CRF was started were accounted for in the study report.

Efficacy analyses were based on the Full Analysis Set (FAS), which was defined as all randomised subjects. A per protocol (PP) analysis set was used as an efficacy subset and was defined as subjects in the FAS who completed the trial without major protocol deviations. Analysis based on the FAS was considered the primary analysis, whereas the PP analysis served a supportive purpose. Safety analyses were based on the Safety analysis set, which was defined as all subjects who received at least 1 application of trial medication and had safety information available post treatment.

Randomisation was stratified by trial site. In order to aim at obtaining at least 2 subjects per site per treatment group, trial sites yielding fewer than 8 subjects was combined into “analysis sites” having at least 8 subjects in order of geographical proximity. The exact composition of these analysis sites is described in the SAPU (Appendix 1.9).

Only completed treatment groups were tested for efficacy, i.e. efficacy data from the 4-day active treatment group closed after the safety interim analysis was tabulated, but not analysed.
6.2.2 Subject Disposition

Frequencies of the analysis sets, in total and by treatment group, were tabulated. Reasons for premature discontinuation from treatment and from the trial were presented for the FAS population and the reasons for leaving the study were also presented by last visit.

6.2.3 Baseline Characteristics

Descriptive statistics of demographic and other baseline characteristics were presented for the FAS. Demographics included age, sex, race, ethnic origin and skin type. Other baseline characteristics included height, weight, vital signs, other diagnoses and concomitant medication. Baseline AK characteristics included treatment location and baseline lesion count for the treatment area.

Additional descriptive statistic tables, not described in the clinical study protocol, were added in the SAPU: Number of AK lesion at baseline by analysis site, baseline composite LSR score by country and anatomical location, AK duration by country and overall, AK treatment history inside and outside treatment areas, skin disease history inside and outside treatment areas and non-melanoma skin cancer history.

Subject CRF no. PPDD was planned to be treated on “Arm including back of hand” but was finally treated on Arm only (not including back of hand) based on subject decision. This subject was considered as a subject treated on “Arm not including back of hand” in all analyses.

6.2.4 Efficacy Analysis

6.2.4.1 Primary Efficacy Criterion

As the primary analysis a Cochran-Mantel-Haenszel test adjusting for analysis site was performed. To account for multiple testing, the three tests comparing an active group with the vehicle group were performed using a closed test procedure. The pre-defined hierarchical order of testing was determined as follows in the clinical study protocol:

- The 4-day active application treatment group was to be tested first and provided a significant result was observed, the 3-day active application treatment group was to be tested, and finally the 2-day active application treatment group was to be tested thus securing that the overall significance level did not exceed 5%.

As the 4-day active application treatment group was closed before completion of enrollment for the trial, it was removed from the models and statistical comparisons according to the clinical study protocol. Consequently, the hierarchical testing strategy was as follows:
The 3-day active application treatment group was to be tested first and provided a significant result was observed, the 2-day active application treatment group was to be tested thus securing that the overall significance level did not exceed 5%.

The primary response criterion was analysed as described in the clinical study protocol Section 10.9.4 (Appendix 1.1) apart from changes described in Section 6.3. Clarification of the analysis of primary response due to the use of Multiple Imputation (MI) to handle missing data, is described in the following (see also Section 6.2.6.5).

- For the primary analysis, each of the imputed datasets were to be analysed by calculating the Mantel-Haenszel odds ratio (OR) adjusted for analysis site and its 95% confidence interval (CI). A log transformation was to be applied to the estimated ORs in order to apply Rubin’s pooling methodology (30). The standard error of the transformed estimates was to be obtained from the log-transformed lower and upper confidence limits for the OR estimate as \((\log(\text{upper})-\log(\text{lower}))/2*1.96\). Combined inference for the log transformed ORs was to be obtained using SAS® PROC MIANALYZE, and the combined estimates were to be back-transformed to the original scale. In case of complete data (FAS using observed cases, LOCF and worst case scenario and also PP), the dataset was to be analysed as described above for a single dataset, supplemented with a p-value for the Mantel-Haenszel test of \(\text{OR} = 1\).

- For the secondary analysis, each imputed dataset with complete clearance of AKs at Week 8 was to be analysed by a log binomial regression model with factors: treatment group, analysis site and the interaction between treatment group and analysis site. The number of baseline lesions was to be included as a continuous variable. The multiple chi-square statistics for testing the effect of the interaction between treatment group and analysis site was to be combined into an overall p-value using the approach of Li et al. (31). The estimated rate ratios (RRs) were to be log transformed and combined using Rubin’s pooling methodology as described for the ORs above. The rate ratios of each active group and the vehicle group were to be presented together with their 95% confidence intervals. The analysis in this model was considered exploratory and was to be performed to investigate the interaction between treatment group and analysis site.

In addition, the number and percentage of subjects with complete clearance was tabulated by treatment group and the tabulation was based on the average over imputations.

The primary analysis was based on the FAS with the PP analysis set as a supportive analysis (without any imputation method required as subjects without Visit 7 data were excluded from PP Analysis Set).
Three sensitivity analyses were performed as described in Section 6.2.6.5.

6.2.4.2 Secondary Efficacy Criteria

Secondary response criteria were analysed as described in the clinical study protocol (Sections 10.9.5 and 10.9.6, Appendix 1.1) for the FAS only. As the 4-day active application treatment group was closed before completion of enrollment for the trial, it was removed from the models and statistical comparisons according to the clinical study protocol. Consequently, the hierarchical testing strategy was as follows:

- First reduction in AK count from baseline to Week 8 was to be tested comparing the 3-day active application treatment group with vehicle and then partial clearance was to be tested for the 3-day active application treatment group. Provided the tests were significant, the procedure was to be repeated for the 2-day active application treatment group.

Partial clearance of AKs at Week 8, defined as at least 75% reduction from baseline in number of AKs, was analysed in the same way as the primary response criterion.

For reduction in AK count, missing AK count values were imputed sequentially from the MI model described in Section 6.2.6.5.

Observed means of AK count and observed means of percentage change from baseline in AK were tabulated by treatment group. The tabulation was based on the average over imputations.

For each imputed dataset, AK count at Week 8 was analysed by a negative binomial regression model with treatment group and analysis site as covariates and log baseline AK count as offset. For each dataset the RRs was estimated. The estimated RRs was log transformed and combined using Rubin’s pooling methodology as described for the ORs of the primary response criterion.

Three sensitivity analyses were performed as described in Section 6.2.6.5. Observed means, adjusted means, adjusted percentage reductions with their 95% confidence interval and ratios of adjusted means with their 95% confidence interval were calculated from the model of negative binomial regression.

6.2.4.3 Subgroup Analyses by Anatomical Location

The number of subjects with complete clearance and partial clearance as well as a summary of the reduction in AK count from baseline to Week 8 was tabulated by anatomical location (arm/leg/trunk). No formal hypotheses were tested in these subgroups. In addition, tabulations were made for arm and back of hand separately. In these tabulations subjects may appear in
both groups, since a treatment area can span across both arm and back of hand, but separate
AK counting was performed for these areas.

6.2.5 Safety Analysis

6.2.5.1 Exposure

The number of days with investigational product applications was tabulated including a
footnote describing the unique subject (CRF no. PPD) who received a partial dose (only 1
tube at Day 1 and Day 2).

6.2.5.2 Drug Accountability

Not applicable.

6.2.5.3 Adverse Events

Reporting of adverse events was based on the safety analysis set.

AEs were coded during the course of the study in accordance with the current version of the
Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by Preferred Terms
(PT) and System Organ Class (SOC). The number of subjects experiencing each type of AE
(according to MedDRA PT and SOC) was tabulated regardless of the number of times each
AE was reported by each subject. AEs where the investigator did not exclude a causal
relationship to study medication (i.e., not described relationship as “not related”, adverse drug
reactions) were evaluated separately. As with AEs, the number of subjects affected, not the
number of events, was considered. The causal relationship of AEs to investigational product
and the intensity of AEs were tabulated. Where there were several recordings of causal
relationship and intensity for the same event, causal relationship was taken from the last
report of the event (since that was when the investigator was in possession of most
information and so best able to judge causal relationship) and intensity was taken as the worst
ever recording.

An overall summary of the number (percent) of subjects with any treatment emergent adverse
events (TEAEs), SAEs, premature discontinuations from treatment or from the trial due to
adverse events, treatment related AEs, AEs within treatment area, severe AEs (maximum
intensity indicated as severe in the CRF) was presented.

SAEs and discontinuations from trial or from treatment due to AEs/LSRs was tabulated
and/or listed separately.
The following tables not specifically described in the clinical study protocol was added in the SAPU: most common (≥5%) adverse events and adverse drug reactions, non-serious adverse events by SOC and preferred term, application site events by Lowest Level Term (LLT), and intensity of application site events by LLT.

### 6.2.5.4 Local Skin Responses

The incidence and grade of LSRs was summarised by treatment group overall at each visit and by anatomical location (arm/leg/trunk). Local skin response grades were summarised by frequency counts and descriptive statistics by treatment group for each of the 6 individual LSRs: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration.

A composite (sum) score was obtained by summing the 6 individual LSR scores at each visit. The composite score and change from Baseline were summarised by treatment group at each visit using descriptive statistics. The maximum composite LSR score across visits and the visit of occurrence of the maximum composite LSR score were tabulated by treatment group. The visit where the composite LSR score was less than or equal to the composite score at Baseline was tabulated by treatment group.

LSRs were converted into MedDRA preferred terms applying the conversions seen in Table 5. These AEs were reported separately from AEs recorded on the AE form in the CRF.

#### Table 5 Conversion of LSRs to MedDRA Preferred Terms

<table>
<thead>
<tr>
<th>LSR Term</th>
<th>LSR Grade</th>
<th>MedDRA Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>1-4</td>
<td>Application site erythema</td>
</tr>
<tr>
<td>Flaking/Scaling</td>
<td>1-4</td>
<td>Application site exfoliation.</td>
</tr>
<tr>
<td>Crusting</td>
<td>1-4</td>
<td>Application site scab</td>
</tr>
<tr>
<td>Swelling</td>
<td>1-4</td>
<td>Application site swelling</td>
</tr>
<tr>
<td>Vesiculation/Pustulation</td>
<td>1</td>
<td>Application site vesicles</td>
</tr>
<tr>
<td></td>
<td>2-4</td>
<td>Application site pustules</td>
</tr>
<tr>
<td>Erosion/Ulceration</td>
<td>1-3</td>
<td>Application site erosion</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Application site ulcer</td>
</tr>
</tbody>
</table>

### 6.2.5.5 Laboratory Safety Examinations

A listing and tables of abnormal haematology and biochemistry laboratory values was presented, summarised for each visit at which laboratory analyses were performed using observed cases.
6.2.5.6 Other Assessments

A listing of abnormal ECG parameters was presented and change in ECG parameters from Baseline to Visit 3 was summarised using observed cases. ECG results were summarised and evaluated in a separate ECG Safety Report (Additional Related Reports).

Patient reported outcomes were used as exploratory endpoints. See the SAPU for detailed description and below for overview description:

- TSQM transformed scores were summarised for each domain (effectiveness, side effects, convenience and overall satisfaction) at Week 8. The responses were treated as a continuous variable and analysed using analysis of variance with treatment group and analysis site as factors to test for treatment effect.
- The distribution of the subject’s experience with burning sensation (5 categories) and the onset and duration of burning sensation was tabulated by treatment group and day.
- The correlation between the subject’s experience with burning sensation (5 categories) and the TSQM overall satisfaction domain at Week 8 was investigated using descriptive methods in the subgroup of subjects receiving active treatment.
- Change from baseline in individual photo-damage characteristics was summarised.
- Investigator’s global photo-damage outcome score was summarised by frequency counts and mean score and the subject’s cosmetic outcome scores was summarised by frequency counts.
- Vital signs by visits and change in vital signs from baseline to week 8 was tabulated.

6.2.6 General Principles

All the analyses specified in the clinical study protocol were reviewed in relation to the blinded data actually obtained and the SAPU was finalised before breaking the randomisation code.

6.2.6.1 Pooling of Trial Sites

Trial sites yielding fewer than 8 subjects were combined together into “analysis sites” in order of geographical proximity to obtain at least 2 subjects per site per treatment group. Five sites among 13 in Australia and 9 sites among 14 in United States randomised less than 8 subjects.

In Australia, sites PPD 4 (4 randomised) and PPD 5 (5 randomised) both in Western Australia were pooled together. Sites PPD 1 (1 randomised), PPD 5 (5 randomised), and PPD 7 (7 randomised) in Victoria and New South Wales regions were pooled together.
In United States, sites PPD (2 randomised), PPD (5 randomised), PPD (5 randomised) and PPD (3 randomised) in New York, Maryland and Connecticut were pooled together. Sites PPD (1 randomised), PPD (7 randomised), PPD (7 randomised), PPD (4 randomised) and PPD (3 randomised) in Florida, Oklahoma, and Louisiana regions were pooled together.

6.2.6.2 Handling of Dropouts and Missing Values

Subjects having missing lesion counts are listed below. Missing Visit 7 lesion count were imputed in the primary analysis using a multiple imputation process.

V6: PPD, PPD, PPD, and PPD
V6 and V7: PPD, PPD, PPD, and PPD
V7: PPD

A multiple imputation method was used for the primary and secondary endpoints to handle missing data as described in Section 6.2.6.5.

The 4 subjects (4091, 4122, 4185 and 4222) without Visit 6 assessment but with Visit 7 assessment were excluded before the multiple imputation was performed to obtain a monotone missing data pattern. Missing values were only imputed for the subset of subjects with a monotone missing pattern, as AK count from Visit 6 (the only intermediate visit with AK assessment) was not a part of the analysis. The values for these 4 subjects were re-included to the imputed data set at each imputation level before analysing the multiple imputed data.

Three sensitivity analyses were performed as described in Section 6.2.6.5.

6.2.6.3 Interim Analysis and Data Monitoring

Please see Section 5.1.2 for a description of the safety interim analyses.

6.2.6.4 Multiplicity Adjustments

A closed testing procedure was used to account for multiplicity.

6.2.6.5 Multiple imputation

A multiple imputation method was used for the primary and secondary efficacy endpoints. The imputation method relied on an assumption that the missing data were missing at random (MAR), i.e. that the probability that an observation was missing could depend on observed data but was unrelated to the data not observed. Also a monotone missing data pattern was
assumed, i.e. if an observation was missing at a given visit it was also missing at all subsequent visits (observed missing data and method used to deal with non-monotone distribution of missing data is detailed in Section 6.2.6.2).

Missing values for AK count were imputed sequentially from a negative binomial regression model with treatment group, AK counts at the previous visit, and analysis site as covariates and log baseline AK count as offset using a “mi impute monotone” procedure within STATA® 13.1. One thousand imputations were to be performed. The seed used for imputation of missing data was defined before unblinding as 1235 and the analysis of multiple imputed datasets was performed with SAS® 9.3. Complete clearance and partial clearance were derived from the imputed AK count values.

Three sensitivity analyses were performed for complete clearance, partial clearance and AK count reduction. Out of these, one analysis used only observed data, one analysis used the last observation carried forward method (LOCF) and one analysis used a worst case approach. In the worst case approach, subjects with missing Visit 7 data in the active treatment groups were set to “Not cleared”, “Not partly cleared” and with “baseline AK count value” for complete clearance, partial clearance and AK count, respectively. Missing data in the vehicle group was set to “Cleared”, “Partly cleared” and “0” for complete clearance, partial clearance and AK count, respectively.

6.3 Changes to the Statistical Analysis Plan

Changes to the conduct of the planned protocol analyses are detailed in the SAPU and changes to the SAPU are detailed below:

- The primary analysis was not produced with OR but instead, each of the imputed datasets was analysed by calculating the rate ratio (RR) as it was initially planned in protocol. Fisher's exact tests were produced (except in the multiple imputation model) in addition to the planned CMH for analysis of complete clearance, due to low cell counts as supportive analyses.

The following tables were added, updated, or removed after unblinding of the trial data:

- Secondary statistical analysis of complete clearance of AK at week 8 (observed case) and Secondary statistical analysis of partial clearance at week 8 (observed case) were excluded as these supplementary analyses were not considered relevant as the pre-defined 3-step hierarchical order of statistical testing was not met for the primary endpoint.
• Tables of absolute reduction in AK count by visit, reduction in AK count 8 weeks after treatment by baseline count class, and complete clearance of AK 8 weeks after treatment by baseline AK count class were added.

• Table of ‘Application site events by SOC and LLT’ was changed to ‘Application site pain by LLT’. The rationale was to show that the MedDRA preferred term ‘application site pain’ was coded to ‘application site pain’ and ‘application site burning’ in the LLT. The table of intensity of these events had the corresponding change.

• Table of maximal local skin response post baseline by individual categories was added to describe the incidence per maximal LSR score and individual LSR category.

• Table of maximum burning sensation was added to present maximal burning sensation by country.

• Tables with regression analysis parameters of global satisfaction (TSQM) versus maximal burning and with regression analysis parameters of global satisfaction (TSQM) versus maximal duration for the two high levels combined were added for statistical analysis of the data depicted in corresponding figures. A subject belongs in the low score group if all scores are 2 or 3. A subject with at least one score >3 belongs to the high score group. The longest duration of the highest score observed was used in the analyses.

• Table of neoplasm adverse events in the treatment area was added for description purpose.

6.4 Software and Dictionaries

SAS version 9.3 was used to create statistical analyses, listings, tables, and figures.

MedDRA version 15.1 was used for coding of AEs and medical history.

WHO-DD version 2012Q3 was used for coding concomitant medication.

STATA® version 13.1 was used for imputation of missing AK count using a negative binomial regression model.
7 Trial Population

7.1 Disposition of Subjects

A total of 266 subjects were enrolled in the trial and 224 subjects were randomised to the treatment groups: 55 subjects in the 2-day active treatment group; 59 subjects in the 3-day active treatment group; 49 subjects in the 4-day active treatment group; and 61 subjects in the vehicle group. 132 subjects were randomised by 13 trial sites in Australia and 92 subjects were randomised by 14 trial sites in the US (EoT Table 1-1). Figure 2 shows the visit attendance in the treatment groups. The completion rate was high and similar among all treatment groups (>95%) and all randomised subjects received treatment and were included in the full analysis set and safety analysis set (see Section 7.3). The reasons for withdrawal from the trial are presented in Table 6. A total of 5 subjects were withdrawn from the trial: 2 subjects were lost to follow-up and 1 subject each had withdrawal due to unacceptable AE (pneumonia, not related to treatment), voluntary reason, or other reason (the subject thought that he had received ‘placebo’ and therefore wanted to withdraw from the trial). The vehicle group had most withdrawals (3 subjects), followed by the 3-day and 4-day active treatment groups (1 subject each). No subjects were withdrawn in the 2-day active treatment group.

The first subject was enrolled on 03-Feb-2014 and the last subject’s last visit was on 22-Aug-2014. The study period was balanced between the countries (EoT Table 1-2) and the individual visit dates are listed in Appendix 2.4, Listing 4-4.

Table 6 Reasons for withdrawal from trial: full analysis set

<table>
<thead>
<tr>
<th>Withdrawal reason</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Withdrawals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unacceptable adverse events</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Voluntary (and no other reason)</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Other reason(s)¹</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total number of withdrawn subjects</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Completers</td>
<td>55</td>
<td>100.0</td>
<td>58</td>
<td>98.3</td>
</tr>
</tbody>
</table>

¹ Subject thought he received Placebo and did not want to complete the trial

Cross-reference: End of Text (EoT) Table 1-3
Figure 2  Visit attendance by treatment: full analysis set

Vehicle

Ingenol 4 days

Ingenol 3 days

Ingenol 2 days

All subjects


Cross-reference: EoT Figure 1-1
7.2 Protocol Deviations

A listing of the protocol deviations during the trial conduct is in Appendix 2.2, Listing 2-1. All comments made in the comment field in the CRF are in Appendix 2.2, Listing 2-2. The deviations log was also reviewed to ascertain protocol deviations.

Protocol deviations that lead to exclusion of subject data from the PP analysis sets are summarised for the FAS in Table 7. More details about subject data that was excluded from the PP analysis sets are available in Section 7.3.
### Table 7  Protocol deviations leading to exclusion from per protocol analysis set: full analysis set

<table>
<thead>
<tr>
<th>Protocol deviation</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deviation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature withdrawal</td>
<td>0 0.0</td>
<td>1 1.7</td>
<td>1 2.0</td>
<td>3 4.9</td>
</tr>
<tr>
<td>Did not apply full dose</td>
<td>1 1.8</td>
<td>6 10.2</td>
<td>6 12.2</td>
<td>4 6.6</td>
</tr>
<tr>
<td>Disallowed medication used</td>
<td>1 1.8</td>
<td>1 1.7</td>
<td>5 10.2</td>
<td>2 3.3</td>
</tr>
<tr>
<td>Biopsy within STA</td>
<td>1 1.8</td>
<td>1 1.7</td>
<td>2 4.1</td>
<td>0 0.0</td>
</tr>
<tr>
<td><strong>Total number of subjects</strong></td>
<td>3 5.5</td>
<td>8 13.6</td>
<td>11 22.4</td>
<td>6 9.8</td>
</tr>
</tbody>
</table>

Cross-reference: EoT Table 1-20
Inclusion and Exclusion Criteria

One subject (Subject No. PPD) violated exclusion criterion 20 (treatment with 5-fluorouracil (5-FU), imiquimod, ingenol mebutate, topical diclofenac sodium, or photodynamic therapy) and this was noted after the subject had been randomised and had completed the trial.

Procedure Compliance Deviations

Exclusion from the PP Analysis Set

The following protocol deviations led to exclusion of subject data from the PP analysis set:

- 5 subjects had premature withdrawal
- 17 subjects did not apply full dose of the investigational product
- 9 subjects used disallowed medication
- 4 subjects had a biopsy performed within the treatment area

The 4-day active treatment group had most subjects with protocol deviations (11 subjects, 22.4%), followed by the 3-day active treatment group (8 subjects, 13.6%), the vehicle group (6 subjects, 9.8%), and the 2-day active treatment group (3 subjects, 5.5%). As some subjects had several deviations leading to exclusion the total number of subjects with protocol deviations is lower than the summarised number of subjects for each protocol deviation.

Details of protocol deviations that led to subject data being excluded from the PP analysis set are available in Section 7.3.3. All other protocol deviations were minor and did not lead to exclusion of subject data from the PP analysis set.

Other Protocol Deviation of Interest

The following protocol deviation did not lead to exclusion from the PP analysis set.

Unintended Unblinding of Subject Data

Due to a misunderstanding between the clinical trial supply CRO and the sponsor, treatment group allocations for 10 subjects were transferred to LEO during the conduct of the trial. Data for 8 of these subjects were available in the statistical repository for a period of 10 days until the mistake was discovered. The data was not extracted from the files.

7.3 Trial Analysis Sets

Three trial analysis sets were defined and are described in Sections 7.3.1, 7.3.2, and 7.3.3. The trial analysis sets are graphically presented by treatment group in Figure 3.
Listings of the trial analysis sets and reasons for exclusion from analysis sets are in Appendix 2.3, Listings 3-1 and 3-2, respectively.

**Figure 3**  
**Trial analysis sets by treatment: full analysis set**

![Diagram illustrating trial analysis sets by treatment: full analysis set](image)

**7.3.1 Full Analysis Set**

The Full Analysis Set (FAS) was defined as all randomised subjects and the efficacy analyses were based on the FAS.

A total of 224 subjects were randomised. The FAS consisted of 224 subjects but subjects in the 4-day active treatment group were excluded from the analysis and statistical comparisons according to the clinical study protocol (Appendix 1.1, Section 10.9.1).

**7.3.2 Safety Analysis Set**

Safety analyses were based on the safety analysis set, which was defined as all subjects who received at least 1 application of investigational product and had safety information available post treatment.

All randomised subjects applied at least 1 dose of treatment and had safety information available post treatment. Thus, the safety analysis set consisted of 224 subjects.
7.3.3 Per Protocol Analysis Set

The per protocol (PP) analysis set was used as an efficacy subset defined as subjects in the FAS who completed the trial without major protocol deviations. The efficacy analyses based on the PP analysis set were performed to support the corresponding results obtained for the FAS.

Randomisation in the 4-day active treatment group was discontinued after the final safety interim analysis based on the DMC recommendation. Data from this treatment group was included in PP tabulations but excluded from all statistical comparisons and models according to the clinical study protocol (Appendix 1.1, Section 10.9.1).

Deviations Leading to Exclusion from the PP Analysis Set

An asterisk (*) indicates that a subject has multiple deviations and has been excluded for a reason already stated.

A total of 28 subjects were excluded from the PP analysis set:

- 5 subjects were prematurely withdrawn from the trial before Visit 7:
  - Lost to follow-up (2 subjects, Subject No. PPD and PPD)
  - Withdrawn for voluntary reason (1 subject, Subject No. PPD)
  - Withdrawn for other reason (1 subject, Subject No. PPD)
  - Unacceptable AE (Pneumonia, Subject No. PPD)

- 17 subjects did not apply correct amount of investigational product according to protocol (whereof 3 *subjects, PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, and PPD)

- 9 subjects received concomitant medication violating the requirements (whereof 4 *subjects):
  - Liquid nitrogen within the treatment area (1 subject, Subject No. PPD)
  - Antibiotic and corticosteroids within the treatment area (1 subject, Subject No. PPD *)
  - Non medicated lotion within the treatment area during treatment days (2 subjects, Subject No. PPD * and PPD *)
  - Creams within the treatment area (1 subject, Subject No. PPD *)
Corticosteroids and other dermatological products within the treatment area (1 subject, Subject No. PPD)

Systemic corticosteroids and photodynamic therapy (1 subject, Subject No. PPD)

Imiquimod during trial (2 subjects, Subject No. PPD and PPD)

- 4 subjects were biopsied within the treatment area (Subject No. PPD, PPD, and PPD).

Thus, the PP analysis set consisted of 196 subjects but subjects in the 4-day active treatment group were excluded from the statistical analyses.

7.4 Demographic and other Baseline Characteristics

7.4.1 Demographics

The trial population comprised 144 men (64.3%) and 80 women (35.7%). The number of men for each treatment group was 35 (63.6%) in the 2-day active treatment group; 32 (54.2%) in the 3-day active treatment group; 36 (73.5%) in the 4-day active treatment group; and 41 (67.2%) in the vehicle group (Table 8).

The percentage of men had similar range for Australia (range 54.5% to 71.9%) and the US (range 53.8% to 76.5%). Both countries had similar distribution of men in the 3-day- and 4-day active treatment groups, and slightly higher for the US in the 2-day active treatment group and vehicle treatment group compared with Australia (Table 8).

Near all subjects (221 subjects, 98.7%) had Fitzpatrick skin type I to III with skin type II (always burns easily and tans minimally) being the most common (122 subjects, 54.5%). The distribution was similar among the treatment groups (Table 9). The most common skin type in Australia was type I (65 subjects, 49.2%) and in the US type II (64 subjects, 69.6%) (Table 9).

All subjects were white and almost all were self-assessed as non-Hispanic or Latino (223 subjects, 99.6%) (Table 10 and Table 11, respectively).

The mean age was 68.3 years (median 68.0; range 39 to 91), and the mean age did not differ much between the treatment groups and by country (Table 12).

All subjects attended the Baseline physical examination and vital signs (diastolic and systolic blood pressure and heart rate) were measured. All vital sign characteristics had similar distribution among the treatment groups (EoT Table 1-15).
Listings of demographics data and vital signs are provided in Appendix 2.4, Listing 4-1 and Appendix 2.8, Listing 8-3, respectively.
Table 8  
Sex by country and overall: full analysis set

<table>
<thead>
<tr>
<th>Country/sex</th>
<th>All randomised subjects (n=224)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
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<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
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<td></td>
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<td>17</td>
<td>70.8</td>
<td>14</td>
</tr>
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<td>32.6</td>
<td>7</td>
<td>29.2</td>
<td>12</td>
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<td>26</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<td>82</td>
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<td>18</td>
<td>58.1</td>
<td>18</td>
</tr>
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<td>50</td>
<td>37.9</td>
<td>13</td>
<td>41.9</td>
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<td>35</td>
<td>63.6</td>
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<td>27</td>
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Cross-reference: EoT Table 1-9
## Table 9  
Skin type by country and overall: full analysis set

<table>
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<tr>
<th>Country/skin type</th>
<th>All randomised subjects</th>
<th>Ingenol 2 days</th>
<th>Ingenol 3 days</th>
<th>Ingenol 4 days</th>
<th>Vehicle</th>
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<td></td>
<td>(n=224)</td>
<td>(n=55)</td>
<td>(n=59)</td>
<td>(n=49)</td>
<td>(n=61)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I: Always burns easily, never tans</td>
<td>12</td>
<td>13.0</td>
<td>4</td>
<td>16.7</td>
<td>3</td>
</tr>
<tr>
<td>Type II: Always burns easily, tans minimally</td>
<td>64</td>
<td>69.6</td>
<td>15</td>
<td>62.5</td>
<td>19</td>
</tr>
<tr>
<td>Type III: Burns moderately, tans gradually (light brown)</td>
<td>13</td>
<td>14.1</td>
<td>4</td>
<td>16.7</td>
<td>3</td>
</tr>
<tr>
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<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>92</td>
<td>100.0</td>
<td>24</td>
<td>100.0</td>
<td>26</td>
</tr>
<tr>
<td><strong>Australia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I: Always burns easily, never tans</td>
<td>65</td>
<td>49.2</td>
<td>13</td>
<td>41.9</td>
<td>16</td>
</tr>
<tr>
<td>Type II: Always burns easily, tans minimally</td>
<td>58</td>
<td>43.9</td>
<td>14</td>
<td>45.2</td>
<td>15</td>
</tr>
<tr>
<td>Type III: Burns moderately, tans gradually (light brown)</td>
<td>9</td>
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<td>4</td>
<td>12.9</td>
<td>2</td>
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<td>31</td>
<td>100.0</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Type I: Always burns easily, never tans</td>
<td>77</td>
<td>34.4</td>
<td>17</td>
<td>30.9</td>
<td>19</td>
</tr>
<tr>
<td>Type II: Always burns easily, tans minimally</td>
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<td>29</td>
<td>52.7</td>
<td>34</td>
</tr>
<tr>
<td>Type III: Burns moderately, tans gradually (light brown)</td>
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<td>9.8</td>
<td>8</td>
<td>14.5</td>
<td>5</td>
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<td>1.8</td>
<td>1</td>
</tr>
<tr>
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<td>100.0</td>
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</table>

1) n=Number of subjects

Cross-reference: EoT Table 1-10
Table 10  Race by country and overall: full analysis set

<table>
<thead>
<tr>
<th>Country/race</th>
<th>All randomised subjects (n=224)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
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<td>White</td>
<td>92</td>
<td>100.0</td>
<td>24</td>
<td>100.0</td>
</tr>
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<td>92</td>
<td>100.0</td>
<td>24</td>
<td>100.0</td>
<td>26</td>
</tr>
<tr>
<td>Australia</td>
<td>White</td>
<td>132</td>
<td>100.0</td>
<td>31</td>
<td>100.0</td>
</tr>
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<td>Total</td>
<td>132</td>
<td>100.0</td>
<td>31</td>
<td>100.0</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>White</td>
<td>224</td>
<td>100.0</td>
<td>55</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
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<td>55</td>
<td>100.0</td>
<td>59</td>
</tr>
<tr>
<td>Country/ethnic origin</td>
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<td>Ingenol 2 days (n=55)</td>
<td>Ingenol 3 days (n=59)</td>
<td>Ingenol 4 days (n=49)</td>
<td>Vehicle (n=61)</td>
</tr>
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<td>-----------------------</td>
<td>-----------------------</td>
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</tr>
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<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>24</td>
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<td>Australia</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
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<td>31</td>
<td>100.0</td>
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</tr>
<tr>
<td>Total</td>
<td>132</td>
<td>100.0</td>
<td>31</td>
<td>100.0</td>
<td>33</td>
</tr>
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<td>Total</td>
<td>224</td>
<td>100.0</td>
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<td>100.0</td>
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1) n=Number of subjects

Cross-reference: EoT Table 1-12
Table 12  Age by country and overall: full analysis set

<table>
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<tr>
<th>Age (years)</th>
<th>All randomised subjects (n=224)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>66.3</td>
<td>64.9</td>
<td>64.9</td>
<td>69.1</td>
<td>67.0</td>
</tr>
<tr>
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<td>11.0</td>
<td>10.4</td>
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<td>11.1</td>
</tr>
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<td>72.0</td>
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<td>17</td>
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<td>Australia</td>
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<td>70.7</td>
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<td>69.0</td>
<td>70.0</td>
<td>67.5</td>
<td>69.5</td>
</tr>
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<tr>
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<td>224</td>
<td>55</td>
<td>59</td>
<td>49</td>
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</tbody>
</table>

7.4.2 Other Baseline Characteristics

The mean duration of AK was 14.4 years (median 12.0; range 0 to 44), and overall, the mean duration of AK was similar among all treatment groups but higher for Australia compared with the United States in all treatment groups (overall mean was 17.6 years in Australia vs 9.8 years in US) (Table 13). Listings are in Appendix 2.4, Listing 4-2.

More than 90% of the subjects in all treatment groups had been previously treated for AK and the most common treatments in all treatment groups were cryo/liquid nitrogen, surgical excision/curettage, and 5-fluorouracil (Table 14). Fewer subjects had a treatment history of AK lesions in the current treatment area (range 50.8% to 60.0% across the treatment groups) but the most common treatments followed the same trend as for overall treatment history (EoT Table 1-17).

Overall, most subjects had the treatment area located on the arm: 117 subjects (52.2%) had the treatment area located on arm including back of hand, 79 subjects (35.3%) on the arm not including back of hand, 13 subjects (5.8%) on the leg, and 15 subjects (6.7%) on the trunk. The anatomical location distribution was similar among the treatment groups and no major
differences were found between the countries overall and among the treatment groups in each country (Table 15).

Table 13  AK duration by country and overall: full analysis set

<table>
<thead>
<tr>
<th>Duration of AK (years)</th>
<th>All randomised subjects (n=224)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>United States</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<td>9.7</td>
<td>9.4</td>
<td>9.5</td>
<td>10.6</td>
</tr>
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<td>8.3</td>
<td>9.2</td>
<td>10.0</td>
</tr>
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<td>9.0</td>
<td>7.0</td>
<td>9.0</td>
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<td>30</td>
</tr>
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<td>Number</td>
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<td>26</td>
<td>17</td>
<td>25</td>
</tr>
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<td><strong>Australia</strong></td>
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<tr>
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<td>16.0</td>
<td>18.2</td>
<td>18.8</td>
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<td>15.0</td>
<td>17.0</td>
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<td>Maximum</td>
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<td>37</td>
<td>41</td>
<td>39</td>
</tr>
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<td>Number</td>
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<td>33</td>
<td>32</td>
<td>36</td>
</tr>
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<td></td>
<td></td>
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<td>15.2</td>
<td>15.4</td>
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<td>12.4</td>
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<td>12.0</td>
<td>10.0</td>
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</tr>
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</tr>
<tr>
<td>Number</td>
<td>224</td>
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<td>59</td>
<td>49</td>
<td>61</td>
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Cross-reference: EoT Table 1-14
### Table 14  AK treatment history: full analysis set

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<th>AK treatments</th>
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<th></th>
<th>Ingenol 4 days (n=49)</th>
<th></th>
<th>Vehicle (n=61)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Cryo/Liquid nitrogen</td>
<td>53</td>
<td>96.4</td>
<td>54</td>
<td>91.5</td>
<td>45</td>
<td>91.8</td>
<td>59</td>
<td>96.7</td>
</tr>
<tr>
<td>Surgical excision/curettage</td>
<td>33</td>
<td>60.0</td>
<td>25</td>
<td>42.4</td>
<td>24</td>
<td>49.0</td>
<td>27</td>
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</tr>
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<td>1</td>
<td>1.7</td>
<td>1</td>
<td>2.0</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Medium or greater depth chemical peel</td>
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<td>3.6</td>
<td>1</td>
<td>1.7</td>
<td>4</td>
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<td>1</td>
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<td>1.6</td>
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<td>22</td>
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<td>10</td>
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<tr>
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<td>4.1</td>
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<tr>
<td>12% lactic acid</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>12% lactic acid cream</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>25% urea, 2% salicylic acid</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>2.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>3% salicylic acid</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>ALA 20%</td>
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<td>0.0</td>
<td>1</td>
<td>1.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Calmurid cream</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
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<td>1.6</td>
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<tr>
<td>Citra</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
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<td>0.0</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Efudex</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Eлоcon ointment</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Eлоcon ointment and urea based moisturiser</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Eлоcon serum</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Lactic acid cream</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Picato, scalp</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
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<td>1.6</td>
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</table>
Table 14  AK treatment history: full analysis set (continued)

<table>
<thead>
<tr>
<th>AK treatments</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n¹</td>
<td>%</td>
<td>n¹</td>
<td>%</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Salicylic acid and urea emollient</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Urea cream</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Uroderm</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Zyclara</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total number of previous treatments</td>
<td>152</td>
<td>143</td>
<td>129</td>
<td>156</td>
</tr>
<tr>
<td>Total number of previously treated subjects</td>
<td>54</td>
<td>98.2</td>
<td>55</td>
<td>93.2</td>
</tr>
</tbody>
</table>

1) n=Number of subjects

Cross-reference: EoT Table 1-16
## Table 15

Anatomical treatment location by country and overall: full analysis set

<table>
<thead>
<tr>
<th>Country/treatment location</th>
<th>All randomised subjects (n=224)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td><strong>United States</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm including back of hand</td>
<td>43</td>
<td>46.7</td>
<td>12</td>
<td>50.0</td>
<td>11</td>
</tr>
<tr>
<td>Arm not including back of</td>
<td>39</td>
<td>42.4</td>
<td>10</td>
<td>41.7</td>
<td>11</td>
</tr>
<tr>
<td>hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg</td>
<td>2</td>
<td>2.2</td>
<td>1</td>
<td>4.2</td>
<td>0</td>
</tr>
<tr>
<td>Trunk</td>
<td>8</td>
<td>8.7</td>
<td>1</td>
<td>4.2</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>100.0</td>
<td>24</td>
<td>100.0</td>
<td>26</td>
</tr>
<tr>
<td><strong>Australia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm including back of hand</td>
<td>74</td>
<td>56.1</td>
<td>20</td>
<td>64.5</td>
<td>20</td>
</tr>
<tr>
<td>Arm not including back of</td>
<td>40</td>
<td>30.3</td>
<td>8</td>
<td>25.8</td>
<td>9</td>
</tr>
<tr>
<td>hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg</td>
<td>11</td>
<td>8.3</td>
<td>3</td>
<td>9.7</td>
<td>2</td>
</tr>
<tr>
<td>Trunk</td>
<td>7</td>
<td>5.3</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
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<tr>
<td>Total</td>
<td>132</td>
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<td>31</td>
<td>100.0</td>
<td>33</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm including back of hand</td>
<td>117</td>
<td>52.2</td>
<td>32</td>
<td>58.2</td>
<td>31</td>
</tr>
<tr>
<td>Arm not including back of</td>
<td>79</td>
<td>35.3</td>
<td>18</td>
<td>32.7</td>
<td>20</td>
</tr>
<tr>
<td>hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg</td>
<td>13</td>
<td>5.8</td>
<td>4</td>
<td>7.3</td>
<td>2</td>
</tr>
<tr>
<td>Trunk</td>
<td>15</td>
<td>6.7</td>
<td>1</td>
<td>1.8</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>224</td>
<td>100.0</td>
<td>55</td>
<td>100.0</td>
<td>59</td>
</tr>
</tbody>
</table>

1) n=Number of subjects

Cross-reference: EoT Table 1-4
The mean baseline composite LSR score had similar distribution among the treatment groups (mean range 1.5 to 1.7) and was slightly higher in Australia (mean range 1.8 to 1.9) than the United States (mean range 1.1 to 1.4) for the active treatment groups (EoT Table 1-8). Listings are in Appendix 2.7, Listing 7-3.

The mean baseline AK lesion count had a similar distribution across the treatment groups and by anatomical location (arm including back of hand and arm not including back of hand). The mean AK lesion count overall was 12.2 (median 12.0, range 5 to 20) but Australia had higher mean AK lesion count (13.5) than the United States (10.4) with the same trend across all treatment groups. The AK lesion count for leg and trunk had larger differences between the treatment groups, but only few subjects were included in each treatment group (Table 16 and EoT Table 1-7). Patterns in baseline AK lesion count by analysis site were difficult to interpret due to the few subjects included in most analysis sites (EoT Table 1-6). Listings are in Appendix 2.6, Listing 6-1.

Table 16

<table>
<thead>
<tr>
<th>Country</th>
<th>All randomised subjects (n=224)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>10.4</td>
<td>11.2</td>
<td>9.5</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>3.9</td>
<td>4.7</td>
<td>3.7</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>10.0</td>
<td>10.0</td>
<td>9.0</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>20</td>
<td>20</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>92</td>
<td>24</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>13.5</td>
<td>13.5</td>
<td>14.0</td>
<td>13.5</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.4</td>
<td>5.0</td>
<td>4.2</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>13.0</td>
<td>12.0</td>
<td>14.0</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Maximum</td>
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<td>20</td>
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<td>32</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>12.2</td>
<td>12.5</td>
<td>12.4</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.5</td>
<td>4.9</td>
<td>4.6</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>12.0</td>
<td>11.0</td>
<td>12.0</td>
<td>12.0</td>
</tr>
<tr>
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<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>224</td>
<td>55</td>
<td>59</td>
<td>49</td>
</tr>
</tbody>
</table>

More than 80% of the subjects in all treatment groups (range 83.1% to 90.9%) had a history of skin disease with BCC, SCC of skin, and Bowen’s disease as the most common diseases.
Fewer subjects had a skin disease history inside the treatment area (range 13.6% to 18.4% across the treatment groups) but the trend for most common diseases was similar as for overall history of skin disease (EoT Tables 1-18 and 1-19). In addition, more than 75% of the subjects in all treatment groups (range 76.3% to 85.2%) had a history of non-melanoma skin cancer consisting of diagnoses for BCC, SCC of skin, and Bowen’s disease. The trend was similar among the treatment groups (EoT Table 1-24).

More than 80% of the subjects in all treatment groups (range 84.7% to 96.4%) were taking concomitant medication at Baseline. The most common medications across all treatment groups were for the anatomical therapeutic class (ATC) index cardiovascular system and alimentary tract and metabolism (Table 17).

More than 75% of the subjects in all treatment groups (range 76.3% to 87.8%) had at least 1 concurrent diagnosis at Baseline (Table 18). The most common concurrent diagnoses at Baseline were within the SOCs surgical and medical procedures, vascular disorders, and metabolism and nutrition disorders, with similar distribution among the treatment groups (Table 18).

Listings of treatment history, medical history, concurrent diagnoses at Baseline, and concomitant medication are provided in Appendix 2.4, Listings 4-3, 4-5, 4-6, and 4-7.
## Table 17  Concomitant medications at baseline: full analysis set

<table>
<thead>
<tr>
<th>ATC classification index level 1</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Drugs</td>
<td>No. Subj</td>
<td>%</td>
<td>No. Drugs</td>
</tr>
<tr>
<td>Alimentary tract and metabolism</td>
<td>70</td>
<td>35</td>
<td>63.6</td>
<td>60</td>
</tr>
<tr>
<td>Antiinfectives for systemic use</td>
<td>6</td>
<td>5</td>
<td>9.1</td>
<td>0</td>
</tr>
<tr>
<td>Antineoplastic and immunomodulating agents</td>
<td>2</td>
<td>2</td>
<td>3.6</td>
<td>1</td>
</tr>
<tr>
<td>Blood and blood forming organs</td>
<td>18</td>
<td>15</td>
<td>27.3</td>
<td>29</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>92</td>
<td>40</td>
<td>72.7</td>
<td>87</td>
</tr>
<tr>
<td>Dermatologicals</td>
<td>15</td>
<td>9</td>
<td>16.4</td>
<td>5</td>
</tr>
<tr>
<td>Genito urinary system</td>
<td>13</td>
<td>11</td>
<td>20.0</td>
<td>9</td>
</tr>
<tr>
<td>and sex hormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculo-Skeletal system</td>
<td>17</td>
<td>16</td>
<td>29.1</td>
<td>16</td>
</tr>
<tr>
<td>Nervous system</td>
<td>27</td>
<td>18</td>
<td>32.7</td>
<td>31</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>12</td>
<td>10</td>
<td>18.2</td>
<td>26</td>
</tr>
<tr>
<td>Sensory organs</td>
<td>6</td>
<td>4</td>
<td>7.3</td>
<td>0</td>
</tr>
<tr>
<td>Systemic hormonal preparations, excl. sex hormones</td>
<td>6</td>
<td>6</td>
<td>10.9</td>
<td>4</td>
</tr>
<tr>
<td>Various</td>
<td>9</td>
<td>7</td>
<td>12.7</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total number of drugs taken</strong></td>
<td>293</td>
<td>271</td>
<td></td>
<td>191</td>
</tr>
<tr>
<td><strong>Total number of subjects taking drugs</strong></td>
<td>53</td>
<td>96.4</td>
<td></td>
<td>50</td>
</tr>
</tbody>
</table>

1) Drugs with the same Anatomical Therapeutic Chemical (ATC) classification level 4 code and generic name/preferred term name which have been taken by the same subject have been counted as one.

Cross-reference: BoT Table 1-21
Table 18  Concurrent diagnoses at baseline by MedDRA Primary System Organ Class (SOC): full analysis set

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>6</td>
<td>2</td>
<td>3.6</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>11</td>
<td>9</td>
<td>16.4</td>
<td>19</td>
</tr>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>6</td>
<td>6</td>
<td>10.9</td>
<td>4</td>
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<tr>
<td>Eye disorders</td>
<td>6</td>
<td>6</td>
<td>10.9</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>24</td>
<td>20</td>
<td>36.4</td>
<td>16</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>8</td>
<td>7</td>
<td>12.7</td>
<td>3</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>11</td>
<td>10</td>
<td>18.2</td>
<td>10</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>8</td>
<td>7</td>
<td>12.7</td>
<td>4</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>2</td>
<td>2</td>
<td>3.6</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td>13</td>
<td>12</td>
<td>21.8</td>
<td>7</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>36</td>
<td>25</td>
<td>45.5</td>
<td>33</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>25</td>
<td>19</td>
<td>34.5</td>
<td>30</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>8</td>
<td>1</td>
<td>1.8</td>
<td>11</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3</td>
<td>3</td>
<td>5.5</td>
<td>12</td>
</tr>
</tbody>
</table>

Continued...
Table 18 Concurrent diagnoses at baseline by MedDRA Primary System Organ Class (SOC): full analysis set (continued)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>13</td>
<td>9</td>
<td>16.4</td>
<td>12</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3</td>
<td>3</td>
<td>5.5</td>
<td>6</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>5</td>
<td>5</td>
<td>9.1</td>
<td>8</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>7</td>
<td>7</td>
<td>12.7</td>
<td>17</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>16</td>
<td>9</td>
<td>16.4</td>
<td>5</td>
</tr>
<tr>
<td>Social circumstances</td>
<td>4</td>
<td>4</td>
<td>7.3</td>
<td>4</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>43</td>
<td>31</td>
<td>56.4</td>
<td>39</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>30</td>
<td>30</td>
<td>54.5</td>
<td>29</td>
</tr>
<tr>
<td><strong>Total number of diagnoses</strong></td>
<td>291</td>
<td></td>
<td></td>
<td>275</td>
</tr>
<tr>
<td><strong>Total number of subjects</strong></td>
<td>48</td>
<td>87.3</td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1
2) Different diagnoses within the same preferred term and involving the same subject have been counted as one. A subject could appear in multiple classes.

Cross-reference: EoT Table 1-22
8 Exposure and Treatment Compliance

The majority of subjects (208 subjects, 92.9%) applied all 4 treatment doses with investigational product and the treatment compliance was similar for all treatment groups (Table 19).

A listing is provided in Appendix 2.5, Listing 5-1.

Table 19  Number of treatment doses applied: safety analysis set

<table>
<thead>
<tr>
<th>Number of treatment doses</th>
<th>All randomised subjects (n=224)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>1.3</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>1.3</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>4.5</td>
<td>1</td>
<td>1.8</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>208</td>
<td>92.9</td>
<td>54</td>
<td>98.2</td>
<td>54</td>
</tr>
<tr>
<td>Total</td>
<td>224</td>
<td>100.0</td>
<td>55</td>
<td>100.0</td>
<td>59</td>
</tr>
</tbody>
</table>

1) Subject (3-day active group) applied 4 doses but in 5 days as the first dose was used on day 1 and day 2, second dose on day 3, third dose on day 4 and fourth dose on day 5.

Cross-reference: EoT Table 1-23
9 Efficacy Evaluation

The efficacy endpoints were complete clearance, partial clearance, and reduction in AK count in each separate treatment area 8 weeks after treatment. The endpoints were deducted from the clinical assessment of AKs by the investigator. In addition, the investigator assessed global photo-damage outcome and the subject assessments were TSQM and cosmetic outcome. Listings are available in Appendix 2.6, Listings 6-1 and 6-2.

9.1 Primary Efficacy Endpoint

9.1.1 Complete Clearance of AKs at Week 8

The complete clearance rate of AKs 8 weeks after start of treatment is presented graphically in Figure 4, tabulated in Table 20 and the statistical analysis is in Table 21.

The complete clearance was not statistically significantly different in the 3-day active treatment group (5.1%) and vehicle group (0.0%) (p=0.18) in the primary analysis (Table 20 and Table 21). The 4-day active treatment group had the highest complete clearance rate (26.8%), followed by the 2-day active treatment group (12.7%), 3-day active treatment group (5.1%), and the vehicle group (0.0%). The same trend was seen for the PP analysis set (EoT Tables 2-11 and 2-12) and the sensitivity analyses (EoT Tables 2-2 and 2-5 [observed case], EoT Tables 2-3 and 2-6) [worst case scenario], and EoT Tables 2-36 and 2-37 [LOCF]).

The absence of statistically significant difference for the primary comparison (3-day active treatment group versus vehicle group) of the primary endpoint (complete clearance) had consequences on the statistical validity of other comparisons and other endpoints. First, due to the hierarchical methodology planned for the analysis of complete clearance and the absence of a statistically significant difference between the 3-day active treatment group and the vehicle group, statistical significance cannot be claimed for the comparison between the 2-day active treatment group and the vehicle group. It was decided to keep the value of these analyses in the report tables but to consider them exploratory only and not confirmatory as the type I error is not completely controlled for these other comparisons. Similarly, the absence of a statistically significant treatment difference for the primary endpoint has the same impact on the secondary endpoint analyses that also has to be considered exploratory only.
### Table 20  Complete clearance of AK 8 weeks after treatment (multiple imputation): full analysis set

<table>
<thead>
<tr>
<th>Complete clearance at 8 weeks</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>7.0</td>
<td>3.0</td>
<td>13.1</td>
<td>0.0</td>
</tr>
<tr>
<td>No</td>
<td>48.0</td>
<td>56.0</td>
<td>35.9</td>
<td>61.0</td>
</tr>
<tr>
<td>Total</td>
<td>55.0</td>
<td>59.0</td>
<td>49.0</td>
<td>61.0</td>
</tr>
</tbody>
</table>

1) n/1000 from 1000 imputations of AK count at week 8 using a negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset.

Cross-reference: EoT Table 2-1
Table 21  Statistical analysis of complete clearance of AK 8 weeks after treatment (multiple imputation): full analysis set

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>Relative risk a [95% CI] b</th>
<th>P-value c</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ingenol 3 days versus Vehicle d</td>
<td>2.97 [0.60 to 14.74]</td>
<td>P=0.18</td>
</tr>
<tr>
<td>b) Ingenol 2 days versus Vehicle d e</td>
<td>3.51 [1.00 to 12.41]</td>
<td>P=0.051</td>
</tr>
<tr>
<td>c) Ingenol 3 days versus Ingenol 2 days f g</td>
<td>0.47 [0.13 to 1.68]</td>
<td>P=0.25</td>
</tr>
</tbody>
</table>

1) Based on 1000 imputations of AK count at week 8 using a negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset
2) Adjusted for analysis site using Rubin’s pooling methodology after log transformation of RR of each imputation. Complete clearance relative to vehicle group (a and b) and 2-day group (c)
3) CMH logit estimators were used for comparisons with vehicle due to absence of cleared subject in the vehicle group
4) Type I error not controlled
5) Mantel-Haenszel estimators

Cross-reference: EoT Table 2-4

Figure 4  Complete clearance of AKs by treatment group at week 8 (observed cases)

Cross-reference: EoT Figure 2-4

No statistical analyses were conducted for the following summaries of subgroup measurements of complete AK clearance. Note that some differences between the groups would be expected with groups of such small sizes, and that interpretation of the result has to be performed with caution.
The complete AK clearance rate presented by Baseline AK count class was higher for Baseline counts of 5-9 AK lesions than 10-20 AK lesions for all active treatment groups (Table 22).

The complete AK clearance rate was higher for the United States compared with Australia for all active treatment groups (Table 23).

Since few patients were included in most sites variation between sites is not feasible to assess (EoT Table 2-8).
Table 22  
Complete clearance of AK 8 weeks after treatment by baseline AK count class (observed case): full analysis set

<table>
<thead>
<tr>
<th>Baseline count class</th>
<th>Complete clearance</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-9</td>
<td></td>
<td>10-20</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>5</td>
<td>23.8</td>
<td>2</td>
<td>9.5</td>
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<td></td>
<td></td>
<td>16</td>
<td>76.2</td>
<td>19</td>
<td>90.5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>21</td>
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<td>21</td>
<td>100.0</td>
</tr>
<tr>
<td>10-20</td>
<td></td>
<td>2</td>
<td>5.9</td>
<td>1</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>94.1</td>
<td>36</td>
<td>97.3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>34</td>
<td>100.0</td>
<td>37</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>Yes</td>
<td>7</td>
<td>12.7</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>48</td>
<td>87.3</td>
<td>55</td>
<td>94.8</td>
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<tr>
<td></td>
<td></td>
<td>55</td>
<td>100.0</td>
<td>58</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Cross-reference: EoT Table 2-52
Table 23  Complete clearance of AK 8 weeks after treatment by country (observed case): full analysis set

<table>
<thead>
<tr>
<th>Country</th>
<th>Complete clearance</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>No</td>
<td>29.2</td>
<td>7</td>
<td>100.0</td>
<td>17</td>
<td>70.8</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>12.7</td>
<td>7</td>
<td>100.0</td>
<td>48</td>
<td>87.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>No</td>
<td>100.0</td>
<td>31</td>
<td>100.0</td>
<td>35</td>
<td>72.9</td>
</tr>
<tr>
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<td>0.0</td>
<td>0</td>
<td>100.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>No</td>
<td>100.0</td>
<td>84</td>
<td>100.0</td>
<td>93</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>12.7</td>
<td>7</td>
<td>100.0</td>
<td>48</td>
<td>87.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cross-reference: EoT Table 2-10
Complete AK clearance was assessed by anatomical location for arm including back of hand, arm not including back of hand, leg, and trunk. Most subjects were treated on arm including back of hand or arm not including back of hand and too few subjects were treated on the leg or trunk to include these 2 groups in a descriptive comparison of complete AK clearance. The complete AK clearance rate was lower on arm including back of hand (9.4%) than arm not including back of hand (16.7%) in the 2-day active treatment group, similar for arm including back of hand (6.7%) and arm not including back of hand (5.0%) in the 3-day active treatment group, and higher for arm including back of hand (28.6%) than arm not including back of hand (14.3%) in the 4-day active treatment group (Table 24).

In addition, the complete AK clearance was presented for back of hand and arm excluding back of hand (including ‘arm’ results for subjects applied investigational product on the arm not including back of hand and arm including back of hand). The complete AK clearance rate between arm excluding back of hand and back of hand was similar in all active treatment groups: arm excluding back of hand (22.0%) and back of hand (21.9%) in the 2-day active treatment group; arm excluding back of hand (24.0%) and back of hand (23.3%) in the 3-day active treatment group; arm excluding back of hand (33.3%) and back of hand (35.7%) in the 4-day active treatment group (EoT Table 2-42). For both arm excluding back of hand and back of hand the complete AK clearance rate was higher with increased number of treatment days in the active treatment groups (4-day treatment was highest, followed by the 3-day- and 2-day treatments) (EoT Table 2-42).
Table 24  Complete clearance of AK 8 weeks after treatment by anatomical location (observed case): full analysis set

<table>
<thead>
<tr>
<th>Location</th>
<th>Complete clearance</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Arm including back of hand</td>
<td>Yes</td>
<td>3</td>
<td>9.4</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>29</td>
<td>90.6</td>
<td>28</td>
<td>93.3</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>32</td>
<td>100.0</td>
<td>30</td>
<td>100.0</td>
</tr>
<tr>
<td>Arm not including back of hand</td>
<td>Yes</td>
<td>3</td>
<td>16.7</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>15</td>
<td>83.3</td>
<td>19</td>
<td>95.0</td>
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<tr>
<td></td>
<td>Total</td>
<td>18</td>
<td>100.0</td>
<td>20</td>
<td>100.0</td>
</tr>
<tr>
<td>Leg</td>
<td>Yes</td>
<td>1</td>
<td>25.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3</td>
<td>75.0</td>
<td>2</td>
<td>100.0</td>
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<tr>
<td></td>
<td>Total</td>
<td>4</td>
<td>100.0</td>
<td>2</td>
<td>100.0</td>
</tr>
<tr>
<td>Trunk</td>
<td>Yes</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1</td>
<td>100.0</td>
<td>6</td>
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<tr>
<td></td>
<td>Total</td>
<td>1</td>
<td>100.0</td>
<td>6</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>Yes</td>
<td>7</td>
<td>12.7</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>48</td>
<td>87.3</td>
<td>55</td>
<td>94.8</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>55</td>
<td>100.0</td>
<td>58</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Cross-reference: EoT Table 2-9
9.2 Secondary Efficacy Endpoints

Due to the hierarchical methodology planned for the analysis of the primary- and secondary endpoints and the absence of a statistically significant difference between the 3-day active treatment group and the vehicle group for the primary endpoint, statistical significance cannot be claimed for the secondary endpoints (see Section 9.1.1).

9.2.1 Reduction in AK Count from Baseline to Week 8

The reduction in AK count from baseline to Week 8 is presented graphically in Figure 5, tabulated in Table 25 and the statistical analysis is in Table 26.

The 4-day active treatment group had lowest observed mean AK count (3.5), followed by the 3-day active treatment group (4.0, 68.3% reduction from Baseline), the 2-day active treatment group (4.6, 64.5% reduction from Baseline), and the vehicle group (12.0, 11.9% reduction from Baseline) (Table 25). The same trend was seen for the sensitivity analyses (EoT Tables 2-14 and 2-17 [observed case]; 2-15 and 2-18 [worst case]; and 2-40 and 2-41 [LOCF]).

**Table 25** Reduction in AK count 8 weeks after treatment (multiple imputation): full analysis set

<table>
<thead>
<tr>
<th>AK count</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed mean</td>
<td>4.6</td>
<td>4.0</td>
<td>3.5</td>
<td>12.0</td>
</tr>
<tr>
<td>Adjusted mean</td>
<td>4.0</td>
<td>3.6</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Adjusted percentage reduction from baseline</td>
<td>64.5</td>
<td>68.3</td>
<td>11.9</td>
<td></td>
</tr>
</tbody>
</table>

1) Based on 1000 imputations of AK count at week 8 using a negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset
2) From negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset

Cross-reference: EoT Table 2-13
Table 26  
Statistical analysis of AK count 8 weeks after treatment (multiple imputation): full analysis set

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>Ratio of adjusted means¹</th>
<th>[95% CI]¹</th>
<th>P-value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ingenol 2 days versus Vehicle</td>
<td>0.40</td>
<td>[0.32 to 0.51]</td>
<td>P=&lt; 0.001</td>
</tr>
<tr>
<td>b) Ingenol 3 days versus Vehicle</td>
<td>0.36</td>
<td>[0.29 to 0.45]</td>
<td>P=&lt; 0.001</td>
</tr>
<tr>
<td>c) Ingenol 3 days versus Ingenol 2 days</td>
<td>0.89</td>
<td>[0.70 to 1.14]</td>
<td>P=0.36</td>
</tr>
</tbody>
</table>

1) From negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset with 1000 Imputations

Cross-reference: EoT Table 2-16

Figure 5  
Reduction in AK count by treatment group at week 8 (observed cases)

Cross-reference: EoT Figure 2-6

No statistical analyses were conducted for the following summaries of subgroup measurements of reduction in AK count. Note that some differences between the groups would be expected with groups of such small sizes, and that interpretation of the result has to be performed with caution.

The reduction in AK count presented by Baseline AK count class was numerically larger for Baseline counts of 5-9 AK lesions than 10-20 AK lesions for all treatment groups: 2-day: -69.0% and -59.4%; 3-day: -68.2% and -66.0%; 4-day: -78.0% and -71.6%; vehicle: -16.4% and -9.8%, respectively (EoT Table 2-51).
The reduction in AK count was higher for the United States compared with Australia for the 2-day active treatment group (-78.7% and -50.9%, respectively) and the 3-day active treatment group (-73.6% and -61.2%, respectively), but similar for the 4-day active treatment group (-73.4% and -73.7%, respectively) and the vehicle group (-10.0% and -12.7%, respectively) (EoT Table 2-22). The reduction in AK count by analysis site was difficult to interpret due to the few subjects included in most analysis sites (EoT Table 2-20).

By anatomical location the reduction in AK count was lower for arm including back of hand than arm not including back of hand in the 2-day-, 4-day- and vehicle treatment groups (2-day: -61.6% and -66.5%; 4-day: -70.6% and -78.2%; vehicle -11.4% and -15.1%, respectively) while the 3-day active treatment group had the opposite result (-71.7% for arm including back of hand and -62.0% for arm not including back of hand) (EoT Table 2-21).

Overall, the reduction in AK count was larger for arm excluding back of hand than back of hand in all treatment groups. The reduction in AK presented by arm excluding back of hand was largest in the 4-day active treatment group (-74.7%) followed by the 3-day active treatment group (-71.0%), the 2-day active treatment group (-64.6%), and the vehicle group (-10.8%). The corresponding AK reduction for back of hand was largest in the 3-day active treatment group (-68.6%), followed by the 4-day active treatment group (-63.8%), the 2-day active treatment group (-55.9%), and the vehicle group (-7.4%) (EoT Table 2-44).

### 9.2.2 Partial Clearance of AKs at Week 8

The partial clearance of AKs at Week 8 is presented graphically in Figure 6, tabulated in Table 27 and the statistical analysis is in Table 28.

The 4-day active treatment group had highest partial AK clearance rate (60.4%), followed by the 3-day active treatment group (56.2%), the 2-day active treatment group (47.3%), and the vehicle group (2.0%) (Table 27). The same trend was seen for the sensitivity analyses (EoT Tables 2-24 and 2-27 [observed case]; EoT Tables 2-25 and 2-28 [worst case]; and EoT Tables 2-38 and 2-39 [LOCF]).
### Table 27  Partial clearance of AK 8 weeks after treatment (multiple imputation): full analysis set

<table>
<thead>
<tr>
<th>Partial clearance at 8 weeks</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N¹</td>
<td>%</td>
<td>N¹</td>
<td>%</td>
<td>N¹</td>
</tr>
<tr>
<td>Yes</td>
<td>26.0</td>
<td>47.3</td>
<td>33.2</td>
<td>56.2</td>
</tr>
<tr>
<td>No</td>
<td>29.0</td>
<td>52.7</td>
<td>25.9</td>
<td>43.8</td>
</tr>
<tr>
<td>Total</td>
<td>55.0</td>
<td>100.0</td>
<td>59.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

1) N/1000 from 1000 imputations of AK count at week 8 using a negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset

Cross-reference: EoT Table 2-23
Table 28  Statistical analysis of partial clearance of AK 8 weeks after treatment (multiple imputation): full analysis set

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>Relative risk [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ingenol 3 days versus Vehicle</td>
<td>32.26 [ 4.39 to 236.8]</td>
<td>P=&lt; 0.001</td>
</tr>
<tr>
<td>b) Ingenol 2 days versus Vehicle</td>
<td>25.20 [ 3.39 to 187.4]</td>
<td>P=0.002</td>
</tr>
<tr>
<td>c) Ingenol 3 days versus Ingenol 2 days</td>
<td>1.20 [ 0.86 to 1.65]</td>
<td>P=0.28</td>
</tr>
</tbody>
</table>

1) Based on 1000 imputations of AK count at week 8 using a negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset
2) Adjusted for analysis site. Relative risk of partial clearance relative to vehicle group (a and b) and 2-day group (c)
3) Mantel-Haenszel estimators

Figure 6  Partial clearance of AKs by treatment group at week 8 (observed cases)

No statistical analyses were conducted for the following summaries of subgroup measurements of partial clearance in AKs. Note that some differences between the groups would be expected with groups of such small sizes, and that interpretation of the result has to be performed with caution.

The partial AK clearance by analysis site was difficult to interpret due to the few subjects included in most analysis sites (EoT Table 2-30).
By anatomical location the partial AK clearance was similar for arm including back of hand and arm not including back of hand in the 2-day-, 3-day- and vehicle treatment groups (2-day: 46.9% and 50.0%; 3-day: 56.7% and 55.0%; vehicle: 4.2% and 0.0%, respectively) while the 4-day active treatment group had lower partial clearance for arm including back of hand (53.6%) than for arm not including back of hand (71.4%) (EoT Table 2-31). In addition, the partial AK clearance was higher for arm excluding back of hand than back of hand in all active treatment groups (2-day: 60.0% and 40.6%; 3-day: 66.0% and 46.7%; 4-day: 64.3% and 53.6%, respectively) and similar for the vehicle group (2.0% and 4.2%, respectively) (EoT Table 2-43).

9.3 Other Efficacy Observations

9.3.1 Complete Clearance of AKs by Visit

The complete AK clearance rate at Week 4 (Day 31) was similar to Week 8 (Day 56) for the 2-day-, 3-day-, and vehicle treatment groups. The 4-day active treatment group at Week 8 had higher percent subjects with complete clearance than at Week 4 (27.1% vs. 18.8%). The result have to be interpreted with caution due to the low number of subjects with complete clearance at both visits (Figure 7 and EoT Table 2-7).

**Figure 7**  Complete clearance of AKs by treatment group and visit (observed cases)

Cross-reference: EoT Figure 2-1
9.3.2 Reduction in AK Count by Visit

Overall, all active treatment groups had similar percentage reduction in AK count at Week 4 (mean range: -60.4% to -71.1%) compared to Week 8 (mean range: -63.0% to -73.6%), as well as the vehicle group (mean: -12.6% at Week 4 and -11.6% at Week 8) (EoT Table 2-19). The absolute reduction in AK count followed the same trend with similar reduction at Week 4 (mean range -6.9 to -8.9) compared to Week 8 (mean range -7.2 to -9.0) for all active treatment groups and as well as the vehicle group (-1.4 at Week 4 and -1.3 at Week 8) (Figure 8 and EoT Table 2-50).

Figure 8 Reduction in AK count by treatment group and visit (observed cases)

9.3.3 Partial Clearance of AKs by Visit

The partial AK clearance rate was lower at Week 4 compared to Week 8 for the 2-day active treatment group (40.7% and 47.3%, respectively) and 3-day (41.4% and 56.9%, respectively), while the clearance rate was similar for the 4-day active treatment group (60.4% at both time points) and the vehicle group (3.6% and 1.7%, respectively) (Figure 9 and EoT Table 2-29).
9.3.4 Treatment Satisfaction Questionnaire for Medication

The TSQM assessment contained derived scores for effectiveness, side-effects, global satisfaction, and convenience. Evaluation of the TSQM derived scores were performed for the FAS. The TSQM assessment was considered exploratory.

Overall, the questionnaire compliance was ≥98% in the active treatment groups and ranged from 92% to 95% in the vehicle group.

Individual TSQM derived scores are listed per subject in Appendix 2.6, Listing 6-2.

The effectiveness TSQM derived score was statistically significantly higher in the 2-day- and 3-day active treatment groups compared to the vehicle group (mean: 68.4, 67.8, and 37.4, respectively, p<0.001). In addition, the 4-day active treatment group had similar effectiveness score as the other active treatment groups (Table 29).
Table 29  Effectiveness TSQM derived score at end of treatment: full analysis set

<table>
<thead>
<tr>
<th></th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effectiveness score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>68.4</td>
<td>67.8</td>
<td>72.3</td>
<td>37.4</td>
</tr>
<tr>
<td>SD</td>
<td>21.8</td>
<td>24.4</td>
<td>21.1</td>
<td>27.7</td>
</tr>
<tr>
<td>Median</td>
<td>66.7</td>
<td>72.2</td>
<td>77.8</td>
<td>33.3</td>
</tr>
<tr>
<td>Minimum</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Number</td>
<td>55</td>
<td>58</td>
<td>48</td>
<td>56</td>
</tr>
</tbody>
</table>

Comparisons versus vehicle

<table>
<thead>
<tr>
<th></th>
<th>Difference¹</th>
<th>95% CI¹</th>
<th>P-value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30.97</td>
<td>21.67 to 40.26</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>30.38</td>
<td>21.20 to 39.55</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

¹) Least Squares Means difference: From ANOVA with factors: treatment group and analysis site

Cross-reference: EoT Table 2-32
The side effects TSQM derived score was statistically significantly lower in the 2-day- and 3-day active treatment groups compared to the vehicle group (mean: 87.3, 88.3 and 99.9, respectively, p<0.001). In addition, the 4-day active treatment group had similar side effects score as the other active treatment groups (Table 30).

Table 30  Side Effects TSQM derived score at end of treatment: full analysis set

<table>
<thead>
<tr>
<th>Side effect score</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>87.3</td>
<td>88.3</td>
<td>84.9</td>
<td>99.9</td>
</tr>
<tr>
<td>SD</td>
<td>18.8</td>
<td>23.2</td>
<td>22.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>19</td>
<td>6</td>
<td>25</td>
<td>94</td>
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<tr>
<td>Maximum</td>
<td>100</td>
<td>100</td>
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<td>100</td>
</tr>
<tr>
<td>Number</td>
<td>55</td>
<td>58</td>
<td>48</td>
<td>58</td>
</tr>
</tbody>
</table>

Comparisons versus vehicle

| Difference¹ | -12.5                  | -11.5                  |
| 95% CI¹     | -18.92 to -6.14        | -17.81 to -5.20        |
| P-value¹    | < 0.001                | < 0.001                |

¹ Least Squares Means difference: From ANOVA with factors: treatment group and analysis site

Cross-reference: EoT Table 2-33
The global satisfaction TSQM derived score was statistically significantly higher in the 2-day- and 3-day active treatment groups compared to the vehicle group (mean: 64.9, 68.5, and 36.0, respectively, p<0.001). In addition, the 4-day active treatment group had similar global satisfaction score as the other active treatment groups (Table 31).

Table 31  Global Satisfaction TSQM derived score at end of treatment: full analysis set

<table>
<thead>
<tr>
<th></th>
<th>Ingenol 2 days</th>
<th>Ingenol 3 days</th>
<th>Ingenol 4 days</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=55)</td>
<td>(n=59)</td>
<td>(n=49)</td>
<td>(n=61)</td>
</tr>
<tr>
<td><strong>Global satisfaction score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>64.9</td>
<td>68.5</td>
<td>63.5</td>
<td>36.0</td>
</tr>
<tr>
<td>SD</td>
<td>23.7</td>
<td>25.2</td>
<td>24.8</td>
<td>27.7</td>
</tr>
<tr>
<td>Median</td>
<td>64.3</td>
<td>71.4</td>
<td>67.9</td>
<td>35.7</td>
</tr>
<tr>
<td>Minimum</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Maximum</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Number</td>
<td>55</td>
<td>58</td>
<td>48</td>
<td>57</td>
</tr>
<tr>
<td><strong>Comparisons versus vehicle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference (^1)</td>
<td>29.05</td>
<td>32.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI (^1)</td>
<td>19.52 to 38.58</td>
<td>23.24 to 42.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value (^1)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) Least Squares Means difference: From ANOVA with factors: treatment group and analysis site

Cross-reference: EoT Table 2-34
The convenience TSQM derived score was not statistically significantly different in the 2-day- and 3-day active treatment groups compared to the vehicle group (mean: 79.9 (p=0.66), 79.1 (p=0.84), and 78.7, respectively). In addition, the 4-day active treatment group had similar convenience score as the other treatment groups (Table 32).

Table 32  Conveni ence TSQM derived score at end of treatment: full analysis set

<table>
<thead>
<tr>
<th></th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Convenience score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>79.9</td>
<td>79.1</td>
<td>77.7</td>
<td>78.7</td>
</tr>
<tr>
<td>SD</td>
<td>14.8</td>
<td>17.0</td>
<td>14.1</td>
<td>15.3</td>
</tr>
<tr>
<td>Median</td>
<td>83.3</td>
<td>80.6</td>
<td>77.8</td>
<td>77.8</td>
</tr>
<tr>
<td>Minimum</td>
<td>44</td>
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<td>44</td>
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<tr>
<td>Maximum</td>
<td>100</td>
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<tr>
<td>Number</td>
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<td>58</td>
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<tr>
<td><strong>Comparisons versus vehicle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Difference¹</td>
<td>1.28</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI¹</td>
<td>-4.50 to -5.14</td>
<td>-5.14 to -6.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value¹</td>
<td>0.66</td>
<td>0.84</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) Least Squares Means difference: From ANOVA with factors: treatment group and analysis site

Cross-reference: EoT Table 2-35

9.3.5 Investigator’s Global Photo-Damage Outcome at Week 8

Investigator’s global photo-damage outcome assessment at Baseline and Week 8 contained mean scores for the individual photo-damage parameters coarse wrinkling, fine wrinkling, mottled pigmentation, roughness, sallowness, skin laxity, and telangiectasia and mean scores for the global photo-damage outcome. Evaluation of the photo-damage outcome scores and global photo-damage outcome scores were performed for the FAS.

Individual photo-damage outcome scores and global photo-damage outcome scores are listed per subject in Appendix 2.6, Listing 6-3.

Photo-Damage Outcome

Overall, the mean score for all photo-damage parameters was similar across the treatment groups and the reduction from Baseline to Week 8 was slightly larger for the active treatment groups compared to the vehicle group (EoT Table 2-45). Most subjects had photo-damage parameters graded as none, mild or moderate. Three subjects had the most severe grading
reported: 1 subject in the 3-day active treatment group had extreme fine wrinkling at Baseline but not at Week 8, 1 subject in the 2-day active treatment group had extreme mottled pigmentation at Baseline and Week 8, and 1 subject in the 4-day active treatment group had extreme skin laxity at Baseline but not Week 8 (EoT Table 2-46).

**Global Photo-Damage Outcome**

Most subjects in the active treatment groups had improvement (minor, moderate, or marked, at least minor: range 80% to 98% of subjects) in investigator’s global photo-damage outcome at Week 8 and there were no major differences between the treatment groups. Most subjects in the vehicle group had no change (86.4%) in investigator’s global photo-damage outcome. By country, the 2-day- and 3-day active treatment groups had a tendency towards higher outcome score in the United States compared to Australia and the 4-day active treatment group and vehicle group had similar outcome scores in both countries (Table 33). The 4-day active treatment group had highest outcome mean score (1.9), followed by the 3-day active treatment group (1.7), the 2-day active treatment group (1.4), and the vehicle group (0.1) (Table 34).
Table 33  Investigator’s Global Photo-damage outcome frequencies by country: full analysis set

<table>
<thead>
<tr>
<th>Country/Investigator assessment</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=55)</td>
<td>(n=59)</td>
<td>(n=49)</td>
<td>(n=61)</td>
</tr>
<tr>
<td><strong>United States</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor worsening</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No change</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Minor improvement</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Marked improvement</td>
<td>8</td>
<td>12</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>26</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td><strong>Australia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor worsening</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No change</td>
<td>7</td>
<td>6</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Minor improvement</td>
<td>13</td>
<td>9</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>7</td>
<td>16</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Marked improvement</td>
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<td>1</td>
<td>11</td>
<td>1</td>
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<tr>
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<tr>
<td>Minor worsening</td>
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<td>4</td>
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<tr>
<td>Moderate improvement</td>
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<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Marked improvement</td>
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<td>13</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>58</td>
<td>48</td>
<td>59</td>
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</table>

Cross-reference: EoT Table 2-47
Table 34  Investigator’s Global Photo-damage outcome mean score: full analysis set

<table>
<thead>
<tr>
<th>Investigator score</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.4</td>
<td>1.7</td>
<td>1.9</td>
<td>0.1</td>
</tr>
<tr>
<td>SD</td>
<td>1.1</td>
<td>1.0</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>Maximum</td>
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<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Number</td>
<td>55</td>
<td>58</td>
<td>48</td>
<td>59</td>
</tr>
</tbody>
</table>

Cross-reference: EoT Table 2-48

9.3.6 Subject’s Cosmetic Outcome Score

Subject’s cosmetic outcome score assessment at Week 8 contained the outcome parameters ‘overall appearance’ and ‘overall feel’ graded on a scale from ‘worsened’ to ‘much improved’. Evaluation of the cosmetic outcome score was performed for the FAS.

Individual scores for cosmetic outcome are listed per subject in Appendix 2.6, Listing 6-4.

Most subjects in the active treatment groups had improved cosmetic outcome for both overall appearance and overall feel, and most subjects in the vehicle group had no change for both outcome measures. All active treatment groups had similar outcome profile for both overall appearance and overall feel (Table 35).
Table 35  Subject’s cosmetic outcome categories: full analysis set

<table>
<thead>
<tr>
<th>Cosmetic outcome</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Overall appearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>No change</td>
<td>6</td>
<td>10.9</td>
<td>11</td>
<td>19.0</td>
</tr>
<tr>
<td>Somewhat improved</td>
<td>28</td>
<td>50.9</td>
<td>26</td>
<td>44.8</td>
</tr>
<tr>
<td>Much improved</td>
<td>20</td>
<td>36.4</td>
<td>21</td>
<td>36.2</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>100.0</td>
<td>58</td>
<td>100.0</td>
</tr>
<tr>
<td>Overall feel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>No change</td>
<td>15</td>
<td>27.3</td>
<td>16</td>
<td>27.6</td>
</tr>
<tr>
<td>Somewhat improved</td>
<td>20</td>
<td>36.4</td>
<td>20</td>
<td>34.5</td>
</tr>
<tr>
<td>Much improved</td>
<td>19</td>
<td>34.5</td>
<td>21</td>
<td>36.2</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>100.0</td>
<td>58</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Cross-reference: EoT Table 2-49
9.4 Efficacy Conclusions

Complete Clearance, Reduction in AK Count, and Partial Clearance at Week 8

- The complete clearance rate of AKs 8 weeks after start of treatment was not statistically significantly different in the 3-day active treatment group and vehicle group (p=0.18). The 4-day active treatment group had the highest complete clearance rate (26.8%), followed by the 2-day active treatment group (12.7%), 3-day active treatment group (5.1%), and the vehicle group (0.0%) (Section 9.1.1).

- The 4-day active treatment group had lowest observed mean AK count at Week 8 (3.5), followed by the 3-day active treatment group (4.0, 68.3% reduction from Baseline), the 2-day active treatment group (4.6, 64.5% reduction from Baseline), and the vehicle group (12.0, 11.9% reduction from Baseline) (Section 9.2.1).

- The 4-day active treatment group had highest partial AK clearance rate at Week 8 (60.4%), followed by the 3-day active treatment group (56.2%), the 2-day active treatment group (47.3%), and the vehicle group (2.0%) (Section 9.2.2).

- The results for the active treatment groups in reduction in AK count and partial clearance at Week 8 strongly and consistently supported the efficacy of the investigational product.

Treatment Satisfaction Questionnaire for Medication (TSQM)

- Statistically significant difference in the 2-day- and 3-day active treatment groups compared to the vehicle group for effectiveness, side-effects, and global satisfaction TSQM derived scores (p<0.001) and no statistically significant difference between these groups for the convenience TSQM derived score (Section 9.3.4).

- The 4-day active treatment groups had similar TSQM derived scores as the other active treatment groups (Section 9.3.4).

Photo-Damage Outcome

- The mean score for all photo-damage parameters was similar across the treatment groups and the reduction from Baseline to Week 8 was slightly larger for the active treatment groups compared to the vehicle group. Most subjects had photo-damage parameters graded as none, mild or moderate (Section 9.3.5).
Global Photo-Damage Outcome

- Most subjects in the active treatment groups had improvement (minor, moderate, or marked) in investigator’s global photo-damage outcome at Week 8 and there were no major differences between the active treatment groups. Most subjects in the vehicle group had no change in investigator’s global photo-damage outcome (Section 9.3.5)

Cosmetic Outcome Score

- Most subjects in the active treatment groups had improved cosmetic outcome for both overall appearance and overall feel, and most subjects in the vehicle group had no change for both outcome measures (Section 9.3.6)
10 Safety Evaluation

10.1 Adverse Events

10.1.1 Brief Summary of Adverse Events

An overall summary of all AEs is presented in Table 36. The majority of the subjects in the active treatment groups and less than half of the subjects in the vehicle group had AEs. Most AEs in all treatment groups were assessed as mild or moderate and most subjects in the active treatment groups had AEs assessed as related to investigational product by the investigator (‘adverse drug reactions’). The 4-day active treatment group had highest percentage of subjects with related AEs (98.0%) followed by the 3-day-, 2-day-, and vehicle treatment groups (96.6%, 89.1%, and 16.4%, respectively). The most common AEs related to investigational product in all treatment groups were application site pain and application site pruritus (EoT Table 3-5). Most AEs related to the investigational product were recovered/resolved (EoT Table 3-5 and Appendix 2.7, Listing 7-1).

Most subjects in the active treatment groups had AEs in the treatment area: all subjects in the 4-day active treatment group, followed by the 3-day active treatment group (93.2%), and the 2-day active treatment group (89.1%). The most common AE (preferred term) at the application site among all treatment groups was application site pain. In most cases the corresponding LLT was application site burning (EoT Table 3-11).

Twelve subjects had SAEs, whereof most were squamous cell carcinoma (SCC) of skin. Nine out of the 12 SAEs were related to the investigational product and the number of SAEs was similar in the active treatment groups with 3, 5, and 4 in the 2-day-, 3-day-, and 4-day active treatment groups, respectively. No SAEs were reported for the vehicle group.

One unrelated AE of pneumonia lead to withdrawal from the trial (1 subject in the vehicle group). Eight subjects had AEs leading to discontinuation of treatment (including the one that withdrew from the trial): 1 subject in the 2-day active treatment group, 4 subjects in the 3-day active treatment group, 2 subjects in the 4-day active treatment group, and 1 subject in the vehicle group.

There were 12 subjects who reported AEs (including SAEs) within the system organ class ‘neoplasms benign, malignant and unspecified (incl. cysts and polyps)’ for whom follow-up data have been requested. For these 12 subjects (see section 10.1.3 for details) their retrospective medical histories have been requested and the biopsy slides collected have been re-submitted for centralised reassessment and reconfirmation of the diagnoses. These follow-up measures are within the existing protocol and will be reported separately as an addendum to this LP0105-1020 clinical trial report.
Table 36  Overall summary of adverse events: safety analysis set

<table>
<thead>
<tr>
<th>Adverse event category</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of AEs¹</td>
<td>Number of subjects (%)</td>
<td>Number of AEs¹</td>
<td>Number of subjects (%)</td>
</tr>
<tr>
<td>All adverse events</td>
<td>99</td>
<td>49 (89.1)</td>
<td>126</td>
<td>57 (96.6)</td>
</tr>
<tr>
<td>Severe adverse events</td>
<td>1</td>
<td>1 (1.8)</td>
<td>8</td>
<td>6 (10.2)</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
<td>88</td>
<td>49 (89.1)</td>
<td>106</td>
<td>57 (96.6)</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>from trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs on treatment site</td>
<td>76</td>
<td>49 (89.1)</td>
<td>92</td>
<td>55 (93.2)</td>
</tr>
<tr>
<td>SAEs</td>
<td>3</td>
<td>3 (5.5)</td>
<td>5</td>
<td>5 (8.5)</td>
</tr>
</tbody>
</table>

1) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one.

Cross-reference: EoT Table 3-1
10.1.2 Display of Adverse Events

The AEs are summarised by MedDRA primary SOC and preferred term in EoT Table 3-3, by primary SOC in Table 37, and the most common (≥5%) AEs are summarised by primary SOC and preferred term in Table 38. In addition, non-serious AEs are summarised by SOC and preferred term in EoT Table 3-10. Listings are in Appendix 2.7.

Table 37  Adverse events by SOC: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n^1</td>
<td>%</td>
<td>n^2</td>
<td>%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>48 87.3</td>
<td>54 91.5</td>
<td>47 95.9</td>
<td>6 9.8</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>4 7.3</td>
<td>7 11.9</td>
<td>13 26.5</td>
<td>5 8.2</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>3 5.5</td>
<td>6 10.2</td>
<td>7 14.3</td>
<td>7 11.5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>6 10.9</td>
<td>5 8.5</td>
<td>8 16.3</td>
<td>4 6.6</td>
</tr>
<tr>
<td>Investigations</td>
<td>2 3.6</td>
<td>2 3.4</td>
<td>2 4.1</td>
<td>5 8.2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3 5.5</td>
<td>2 3.4</td>
<td>2 4.1</td>
<td>4 6.6</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>2 3.6</td>
<td>3 5.1</td>
<td>1 2.0</td>
<td>2 3.3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1 1.8</td>
<td>2 3.4</td>
<td>3 6.1</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>0 0.0</td>
<td>5 8.5</td>
<td>1 2.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>2 3.6</td>
<td>0 0.0</td>
<td>1 2.0</td>
<td>1 1.6</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>1 1.8</td>
<td>0 0.0</td>
<td>2 4.1</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>0 0.0</td>
<td>2 3.4</td>
<td>1 2.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>1 1.8</td>
<td>1 1.7</td>
<td>1 2.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>0 0.0</td>
<td>1 1.7</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>1 1.8</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
</tbody>
</table>

Total number of adverse events: 99 126 121 39
Total number of subjects: 49 89.1 57 96.6 49 100.0 28 45.9

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
3) n=Number of subjects

Cross-reference: EoT Table 3-2
10.1.3 Analysis of Adverse Events

Adverse Events by Frequency

Overall, the active treatment groups had more AEs than the vehicle group and the percentage of subjects with AEs was higher with increasing number of treatment days: 49 subjects (89.1%) had 99 AEs in the 2-day active treatment group, 57 subjects (96.6%) had 126 AEs in the 3-day active treatment group, and all 49 subjects in the 4-day active treatment group had a total of 121 AEs. Most subjects in the active treatment groups had AEs at the treatment site: all subjects in the 4-day active treatment group, followed by the 3-day active treatment group (93.2%), and the 2-day active treatment group (89.1%) (Table 37).

The most commonly reported AEs among all treatment groups were within the primary SOCs ‘general disorders and administration site conditions’, ‘neoplasms benign, malignant and unspecified (incl. cysts and polyps)’, ‘skin and subcutaneous tissue disorders’, and ‘infections and infestations’ (Table 37).

The most commonly reported AEs in all treatment groups were application site pain and application site pruritus (Table 38). Application site pain is the MedDRA Preferred Term parent to the Lowest Level Term application site burning which was commonly reported in the previous trial LP0105-1012. Therefore, the LLTs of application site pain, is presented in Table 39. Overall, the percentage of subjects with application site burning was highest in the 4-day active treatment group (85.7%), followed by the 3-day active treatment group (83.1%), the 2-day active treatment group (80.0%), and the vehicle group (4.9%).

Neoplasms overall and inside the treatment area

In the SOC ‘neoplasms benign, malignant and unspecified (incl. cysts and polyps)’ 24 subjects had events in the active treatment groups and 5 subjects had events in the vehicle group (Table 37). Most of the AEs in this SOC were SCC of skin, followed by Bowen’s disease, and seborrhoeic keratosis (Table 38). To further elucidate the distribution of SCCs and other potentially cancerous neoplasms in the treatment area all AEs in the neoplasms SOC that were located inside the treatment area were retrieved. The events are presented by preferred term and LLT because intraepidermal carcinoma by LLT map to Bowen’s disease by preferred term and SCC in situ by LLT map to SCC of skin by preferred term. As SCC in situ is synonymous with Bowen’s disease a presentation by both LLT and preferred term provides the most thorough overview. In this textual presentation, 2 cases of seborrhoeic keratosis were not accounted for as seborrhoeic keratosis is noncancerous.

A total of 14 AEs were reported for 12 subjects. The distribution of the 12 subjects reporting the 14 AEs was 4 subjects in each of the 3 active treatment groups. 11 subjects were from
Australia and 10 subjects had a history of skin cancer. Most subjects (8 out of 12) had ≥10 years of duration of AK history (range 0 to 44 years), and most subjects (8 of 12) had an AK count of >10 at Baseline (range 6 to 20). By the LLT, 10 of the 14 AEs were SCC of skin, 2 were keratoacanthoma, 1 was intraepidermal carcinoma, and 1 was squamous cell carcinoma of skin in situ. By preferred term, 11 of the 14 AEs were SCC of skin, 2 were keratoacanthoma, and 1 was Bowen’s disease. All but 1 of these tumours occurred on the arm or hand. The diagnosis was made after a median of 33 days on study. Of these 14 AEs, 12 events were SAEs which were reported for 11 of the 12 subjects (EoT Table 3-38).

For these 12 subjects, retrospective medical histories have been requested and their biopsy slides collected have been re-submitted for centralised reassessment and reconfirmation of the diagnoses to further elucidate these findings. These follow-up measures are within the existing protocol and will be reported separately as an addendum to this LP0105-1020 clinical trial report when these data are available.
Table 38  Adverse events observed in &ge;5% of subjects by SOC and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class (SOC) Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site pain</td>
<td>45</td>
<td>81.8</td>
<td>50</td>
<td>84.7</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>19</td>
<td>34.5</td>
<td>27</td>
<td>45.8</td>
</tr>
<tr>
<td>Application site discomfort</td>
<td>2</td>
<td>3.6</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>SOC total</td>
<td>48</td>
<td>87.3</td>
<td>54</td>
<td>91.5</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma of skin</td>
<td>3</td>
<td>5.5</td>
<td>6</td>
<td>10.2</td>
</tr>
<tr>
<td>Bowen's disease</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Seborrhoeic</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Keratosis</td>
<td>4</td>
<td>7.3</td>
<td>6</td>
<td>10.2</td>
</tr>
<tr>
<td>SOC total</td>
<td>21</td>
<td>7.3</td>
<td>69</td>
<td>18.4</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>SOC total</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>Total number of adverse events</td>
<td>71</td>
<td>89</td>
<td>71</td>
<td>8</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>48</td>
<td>87.3</td>
<td>55</td>
<td>93.2</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Cross-reference: EoT Table 3-4
Table 39  Application site pain by LLT: safety analysis set

<table>
<thead>
<tr>
<th>Lowest Level Term¹</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n³</td>
<td>%</td>
<td>n³</td>
<td>%</td>
</tr>
<tr>
<td>Application site burning</td>
<td>44</td>
<td>80.0</td>
<td>49</td>
<td>83.1</td>
</tr>
<tr>
<td>Application site pain</td>
<td>7</td>
<td>12.7</td>
<td>10</td>
<td>16.9</td>
</tr>
<tr>
<td>Application site stinging</td>
<td>2</td>
<td>3.6</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total number of adverse events³</td>
<td>53</td>
<td></td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>45</td>
<td>81.8</td>
<td>50</td>
<td>84.7</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same lowest level term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
3) n=Number of subjects

Cross-reference: EoT Table 3-11

Adverse Events by Intensity

All AEs were assessed for intensity (mild, moderate, or severe) and presented by SOC and preferred term for all AEs (EoT Table 3-12) and by LLT for application site pain (Table 40).

Overall, most AEs in all treatment groups were assessed as mild or moderate. Among the active treatment groups the 2-day active treatment group had highest number of mild AEs (79), followed by the 3-day active treatment group (74), and the 4-day active treatment group (63). The number of severe AEs was highest in the 4-day active treatment group (8), followed by the 3-day active treatment group (7), and the 2-day active treatment group (1). The vehicle group had 25 mild AEs and no severe AEs. The intensity pattern of the 2 most common AEs, application site pain and application site pruritus, followed the same trend.

The intensity of the LLTs of the most common AE by preferred term, application site pain, is presented in Table 40. The intensity pattern of the most common LLT, application site burning, followed the trend for all AEs. The intensity pattern of the other 2 LLTs was difficult to interpret due to few events.
Table 40  Intensity of application site pain by LLT: safety analysis set

<table>
<thead>
<tr>
<th>Lowest Level Term¹</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mil</td>
<td>Mod</td>
<td>Sev</td>
<td>Mil</td>
</tr>
<tr>
<td>Application site burning</td>
<td>33</td>
<td>11</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Application site pain</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Application site stinging</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total number of adverse events²</td>
<td>40</td>
<td>13</td>
<td>0</td>
<td>29</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same lowest level term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
3) Mod=Moderate, Sev=Severe

Cross-reference: EoT Table 3-13

Adverse Events Related to Investigational Product

The investigator assessed most AEs in the active treatment groups as related to investigational product (adverse drug reactions) and most AEs in the vehicle group were assessed as not related. The 4-day active treatment group had highest percentage of subjects with related AEs (98.0%) followed by the 3-day-, 2-day-, and vehicle treatment groups (96.6%, 89.1%, and 16.4%, respectively). The 3-day active treatment group had the highest number of related AEs (106), followed by the 4-day active treatment group (91), the 2-day active treatment group (88), and the vehicle group (12) (EoT Table 3-14). The most commonly reported related AEs in all treatment groups were application site pain and application site pruritus (Table 41).

Out of the 12 SAEs 9 were related to investigational product and 3 were not related to investigational product (Appendix 2.7, Listing 7-1).

Most AEs related to the investigational product were recovered/resolved, 8 AEs were not recovered/resolved, and they were related to haematology- or biochemistry laboratory values (EoT Table 3-5 and Appendix 2.7, Listing 7-1).
### Table 41  
**Adverse drug reactions observed in >= 5% of subjects by SOC and preferred term: safety analysis set**

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Term</strong></td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site pain</td>
<td>45 81.8</td>
<td>50 84.7</td>
<td>43 87.8</td>
<td>3 4.9</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>19 34.5</td>
<td>27 45.8</td>
<td>14 28.6</td>
<td>2 3.3</td>
</tr>
<tr>
<td>Application site discomfort</td>
<td>2 3.6</td>
<td>3 5.1</td>
<td>2 4.1</td>
<td>1 1.6</td>
</tr>
<tr>
<td>SOC total</td>
<td>48 87.3</td>
<td>54 91.5</td>
<td>46 93.9</td>
<td>6 9.8</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma of skin</td>
<td>2 3.6</td>
<td>3 5.1</td>
<td>3 6.1</td>
<td>0 0.0</td>
</tr>
<tr>
<td>SOC total</td>
<td>2 3.6</td>
<td>3 5.1</td>
<td>3 6.1</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0 0.0</td>
<td>3 5.1</td>
<td>1 2.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>SOC total</td>
<td>0 0.0</td>
<td>3 5.1</td>
<td>1 2.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Total number of adverse events</td>
<td>68 68</td>
<td>86 86</td>
<td>63 63</td>
<td>6 6</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>48 87.3</td>
<td>55 93.2</td>
<td>46 93.9</td>
<td>6 9.8</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse drug reactions within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.  

Cross-reference: EoT Table 3-6
10.2 Deaths, other Serious Adverse Events, and other Significant Adverse Events

10.2.1 Deaths

No deaths were reported.

10.2.2 Other Serious Adverse Events

A total of 12 subjects reported 1 SAE each: 3 subjects in the 2-day active treatment group, 5 subjects in the 3-day active treatment group, 4 subjects in the 4-day active treatment group, and no subjects in the vehicle group (Table 42). The most common SAE was SCC of skin accounting for all SAEs in the 2-day active treatment group, 4 out of 5 SAEs in the 3-day active treatment group, and 3 out of 4 SAEs in the 4-day active treatment group. All SAEs of SCC of skin were inside the treatment area as defined in Section 5.5.4.1. An overview of the in treatment area SCCs and other AEs in the SOC ‘neoplasms benign, malignant and unspecified (incl cysts and polyps)’ is presented in Section 10.1.3. In addition, 1 subject in the 3-day active treatment group had SAE angina pectoris and 1 subject in the 4-day active treatment group had SAE keratoacanthoma (Table 42).

One subject had the AE retinal melanoma assessed as serious by the investigator (Appendix 2.7, Listing 7-1). However, it is not included in the tables of treatment emergent AEs as the event started before first treatment with investigational product (see Section 13).

Narratives of deaths, other SAEs and other significant adverse events are provided end-of-text in Section 13.
Table 42  Serious adverse events by SOC and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(incl cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>3</td>
<td>5.5</td>
<td>4</td>
<td>6.8</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>SOC total</td>
<td>3</td>
<td>5.5</td>
<td>4</td>
<td>6.8</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>SOC total</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Total number of Serious adverse events²</td>
<td>3</td>
<td>5.5</td>
<td>5</td>
<td>8.5</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Cross-reference: EoT Table 3-7
10.2.3 Other Significant Adverse Events

One subject in the vehicle group was withdrawn from the trial due to pneumonia (EoT Table 3-8).

Eight subjects had AEs leading to discontinuation of treatment (including the one that withdrew from the trial): 1 subject in the 2-day active treatment group, 4 subjects in the 3-day active treatment group, 2 subjects in the 4-day active treatment group, and 1 subject in the vehicle group. The most common AE leading to discontinuation of treatment was application site pain (EoT Table 3-9).

Narratives are provided end-of-text in Section 13.

10.3 Vital Signs, Physical Findings and other Observations Related to Safety

10.3.1 Vital Signs and Physical Findings

Descriptive statistics for systolic blood pressure, diastolic blood pressure, heart rate, and body temperature by visit are presented for the FAS in Table 43. Physical examinations were performed at Visits 1, 2, and 7. A listing per subject is in Appendix 2.8, Listing 8-3.

Overall, vital signs (diastolic- and systolic blood pressure, temperature, and heart rate were similar at Baseline compared with Week 8 (Table 43 and EoT Table 3-33). No clinically significant abnormalities relevant for the mostly elderly population in this trial were recorded in the physical examination findings or vital signs during the trial.
Table 43 Vital signs by visit: safety analysis set

<table>
<thead>
<tr>
<th>Vital signs by visit</th>
<th>Innogenol 2 days (n=55)</th>
<th>Innogenol 3 days (n=59)</th>
<th>Innogenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>77.0</td>
<td>76.2</td>
<td>75.1</td>
<td>76.5</td>
</tr>
<tr>
<td>SD</td>
<td>9.9</td>
<td>10.1</td>
<td>10.4</td>
<td>7.3</td>
</tr>
<tr>
<td>Median</td>
<td>77.0</td>
<td>77.0</td>
<td>75.0</td>
<td>75.5</td>
</tr>
<tr>
<td>Minimum</td>
<td>58</td>
<td>55</td>
<td>55</td>
<td>60</td>
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<tr>
<td>Maximum</td>
<td>104</td>
<td>105</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>Number</td>
<td>55</td>
<td>59</td>
<td>49</td>
<td>60</td>
</tr>
<tr>
<td><strong>Day 56</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>78.1</td>
<td>76.5</td>
<td>74.3</td>
<td>75.6</td>
</tr>
<tr>
<td>SD</td>
<td>10.0</td>
<td>10.4</td>
<td>9.0</td>
<td>11.2</td>
</tr>
<tr>
<td>Median</td>
<td>80.0</td>
<td>75.5</td>
<td>74.0</td>
<td>75.0</td>
</tr>
<tr>
<td>Minimum</td>
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<td>95</td>
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<tr>
<td>Number</td>
<td>54</td>
<td>58</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>130.8</td>
<td>129.6</td>
<td>131.1</td>
<td>132.9</td>
</tr>
<tr>
<td>SD</td>
<td>14.9</td>
<td>17.4</td>
<td>21.3</td>
<td>17.1</td>
</tr>
<tr>
<td>Median</td>
<td>129.0</td>
<td>131.0</td>
<td>128.0</td>
<td>132.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>102</td>
<td>98</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Maximum</td>
<td>170</td>
<td>177</td>
<td>200</td>
<td>181</td>
</tr>
<tr>
<td>Number</td>
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<td>59</td>
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<td>60</td>
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<tr>
<td><strong>Day 56</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>130.8</td>
<td>130.0</td>
<td>131.0</td>
<td>132.5</td>
</tr>
<tr>
<td>SD</td>
<td>13.9</td>
<td>17.0</td>
<td>16.2</td>
<td>16.4</td>
</tr>
<tr>
<td>Median</td>
<td>129.0</td>
<td>130.0</td>
<td>130.0</td>
<td>130.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>100</td>
<td>92</td>
<td>100</td>
<td>102</td>
</tr>
<tr>
<td>Maximum</td>
<td>170</td>
<td>161</td>
<td>170</td>
<td>177</td>
</tr>
<tr>
<td>Number</td>
<td>54</td>
<td>58</td>
<td>48</td>
<td>58</td>
</tr>
</tbody>
</table>
Table 43  Vital signs by visit: safety analysis set (continued)

<table>
<thead>
<tr>
<th>Vital signs by visit</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart Rate (Beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>70.3</td>
<td>69.7</td>
<td>67.3</td>
<td>69.5</td>
</tr>
<tr>
<td>SD</td>
<td>8.7</td>
<td>11.7</td>
<td>8.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Median</td>
<td>70.0</td>
<td>70.0</td>
<td>67.0</td>
<td>68.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>54</td>
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<td>45</td>
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<tr>
<td>Maximum</td>
<td>96</td>
<td>91</td>
<td>83</td>
<td>100</td>
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<tr>
<td>Number</td>
<td>55</td>
<td>59</td>
<td>49</td>
<td>61</td>
</tr>
<tr>
<td><strong>Day 56</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>70.6</td>
<td>70.6</td>
<td>69.0</td>
<td>73.0</td>
</tr>
<tr>
<td>SD</td>
<td>8.7</td>
<td>9.1</td>
<td>9.5</td>
<td>12.2</td>
</tr>
<tr>
<td>Median</td>
<td>70.0</td>
<td>69.5</td>
<td>68.0</td>
<td>71.5</td>
</tr>
<tr>
<td>Minimum</td>
<td>55</td>
<td>44</td>
<td>56</td>
<td>45</td>
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<tr>
<td>Maximum</td>
<td>93</td>
<td>90</td>
<td>96</td>
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<tr>
<td>Number</td>
<td>54</td>
<td>58</td>
<td>48</td>
<td>58</td>
</tr>
</tbody>
</table>

| Temperature (C)      |                      |                       |                       |               |
| **Day 1**            |                       |                       |                       |               |
| Mean                 | 36.5                  | 36.4                  | 36.3                  | 36.5          |
| SD                   | 0.3                   | 0.5                   | 0.4                   | 0.4           |
| Median               | 36.4                  | 36.5                  | 36.4                  | 36.6          |
| Minimum              | 36                    | 34                    | 35                    | 35            |
| Maximum              | 37                    | 37                    | 37                    | 38            |
| Number               | 54                    | 58                    | 49                    | 61            |
| **Day 56**           |                       |                       |                       |               |
| Mean                 | 36.5                  | 36.4                  | 36.4                  | 36.5          |
| SD                   | 0.3                   | 0.4                   | 0.4                   | 0.5           |
| Median               | 36.5                  | 36.4                  | 36.5                  | 36.5          |
| Minimum              | 36                    | 35                    | 36                    | 35            |
| Maximum              | 37                    | 37                    | 37                    | 37            |
| Number               | 54                    | 58                    | 48                    | 58            |

10.3.2 Local Skin Response Assessment

The treatment areas (trunk/extremities) were assessed at Day 1 and at each subsequent trial visit for the presence/absence and grade (0 to 4) of the following individual LSRs: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. A composite LSR score (0 to 24), reflecting the sum of the individual LSR grades, was calculated for each treatment area at each visit.

Presentations of LSR scores were produced for the safety analysis set.
10.3.2.1 Composite Local Skin Response Score

Mean composite LSR score versus time is presented by treatment group in Figure 10 and Table 44. The mean composite LSR score peaked at Day 5 in the 3-day- (8.8) and 4-day (11.8) active treatment groups and the 2-day active treatment group had highest LSR scores at Day 5 and Day 10 (7.3). This was followed by a gradual decrease in LSR score at Week 1 (Day 10) (3-day- and 4-day groups) and Week 2 (Day 17), and a return to Baseline score at Week 4 and Week 8. The change in composite LSR score compared to Baseline followed the same trend, with largest change in all active treatment groups at Day 5 (EoT Table 3-21). The vehicle group had similar score at all visits, corresponding to Baseline scores for the active treatment groups (Table 44). No major trends in differences in mean composite LSR score was found by country among all treatment groups (EoT Table 3-22) and by anatomical location for the active treatment groups and the vehicle group. The composite LSR score pattern for the leg and trunk locations was difficult to interpret due to few subjects (EoT Table 3-23).

Most subjects in all treatment groups had the maximal composite LSR score post baseline at Day 5 with highest numbers in the 4-day active treatment group (77.1%), followed by the 3-day active treatment group (62.7%), and the 2-day active treatment group (56.4%). Most subjects in the vehicle group did not have composite LSR scores higher than Baseline at any other visit (66.1%) (Figure 10, Figure 11, and Table 45). The active treatment groups had similar time to return to baseline composite LSR score. Note that some subjects (range 11.9% to 22.9%) did not have a composite LSR score returning to Baseline, but that most of these were 1 composite LSR score unit from returning to Baseline (Table 46).
Figure 10  Mean of composite LSR score versus time by treatment group

Cross-reference: EoT Figure 3-2

Figure 11  Plot of maximum individual and composite LSR score by treatment group

Cross-reference: EoT Figure 3-1
Table 44  
Summary of composite score (LSR) by visit: safety analysis set

<table>
<thead>
<tr>
<th>Visit</th>
<th>Composite LSR score</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Mean</td>
<td>1.5</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
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<tr>
<td></td>
<td>SD</td>
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<td>1.2</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
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<td>0</td>
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<td>Maximum</td>
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<td>6</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>55</td>
<td>59</td>
<td>49</td>
<td>61</td>
</tr>
<tr>
<td>Day 5</td>
<td>Mean</td>
<td>7.3</td>
<td>8.8</td>
<td>11.8</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>3.0</td>
<td>4.3</td>
<td>4.6</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>7.0</td>
<td>9.0</td>
<td>11.5</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
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<td>9</td>
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<td>Number</td>
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<td>Mean</td>
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<td>7.7</td>
<td>9.1</td>
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<td>3.9</td>
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<td>Median</td>
<td>7.0</td>
<td>7.0</td>
<td>9.0</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
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<td>2</td>
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<td></td>
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<tr>
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<td>Number</td>
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<td>59</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td>Day 17</td>
<td>Mean</td>
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<td>4.1</td>
<td>4.5</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>SD</td>
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<td>2.2</td>
<td>1.9</td>
<td>1.2</td>
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<td>Ingenol 4 days (n=49)</td>
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Cross-reference: EoT Table 3-20
### Table 45
Summary of visit of maximal intensity post baseline for composite score (LSR): safety analysis set

<table>
<thead>
<tr>
<th>Parameter/visit</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite LSR score</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>No scores higher than baseline</td>
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<td>1.8</td>
<td>3</td>
<td>5.1</td>
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<tr>
<td>Day 5</td>
<td>31</td>
<td>56.4</td>
<td>37</td>
<td>62.7</td>
</tr>
<tr>
<td>Day 10</td>
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<td>36.4</td>
<td>18</td>
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</tr>
<tr>
<td>Day 17</td>
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<td>1.7</td>
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<tr>
<td>Day 31</td>
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<td>1.8</td>
<td>0</td>
<td>0.0</td>
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<tr>
<td>Day 56</td>
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<td>Total</td>
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<td>100.0</td>
<td>59</td>
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</tr>
</tbody>
</table>
Table 46  Summary of visit of return to baseline for composite score (LSR): safety analysis set

<table>
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<tr>
<th>Parameter/visit</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
</tr>
<tr>
<td>Composite LSR score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No scores higher than baseline</td>
<td>1 1.8</td>
<td>3 5.1</td>
<td>0 0.0</td>
<td>39 66.1</td>
</tr>
<tr>
<td>Day 10</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>1 2.1</td>
<td>4 6.8</td>
</tr>
<tr>
<td>Day 17</td>
<td>8 14.5</td>
<td>7 11.9</td>
<td>3 6.3</td>
<td>3 5.1</td>
</tr>
<tr>
<td>Day 31</td>
<td>19 34.5</td>
<td>20 33.9</td>
<td>16 33.3</td>
<td>4 6.8</td>
</tr>
<tr>
<td>Day 56</td>
<td>17 30.9</td>
<td>20 33.9</td>
<td>17 35.4</td>
<td>2 3.4</td>
</tr>
<tr>
<td>No return to baseline</td>
<td>10 18.2</td>
<td>9 15.3</td>
<td>11 22.9</td>
<td>7 11.9</td>
</tr>
<tr>
<td>Total</td>
<td>55 100.0</td>
<td>59 100.0</td>
<td>48 100.0</td>
<td>59 100.0</td>
</tr>
</tbody>
</table>

1) 5 subjects had maximum value at Day 56 and the remaining subjects had 1 to 3 composite LSR units from a return to baseline: 27 subjects: 1 unit; 4 subjects: 2 units; and 1 subject: 3 units.

Cross-reference: EoT Table 3-25
10.3.2.2 Individual Local Skin Response Components

The individual frequencies of LSR components are presented in EoT Table 3-16 and graphically in Figure 12. In addition, maximal LSR score post baseline by individual category and by country are presented in EoT Tables 3-17 and 3-18, respectively. The LSRs converted to MedDRA SOC and preferred terms (safety analysis set) are presented in EoT Table 3-15.

Individual LSR component scores are listed per subject in Appendix 2.7, Listing 7-3.
Figure 12  Plot LSR category scores versus time by treatment group
Overall, erythema and flaking/scaling were the most common components in all treatment groups. The majority of subjects had erythema and flaking/scaling at Day 1 and the symptoms worsened after starting treatment with a peak at Days 5 and 10, respectively (EoT Table 3-16 and Figure 12).

Overall, around 15% of the subjects in all treatment groups had crusting at Day 1, and most subjects had no other individual LSR components (swelling, vesiculation/pustulation, and erosion/ulceration) at Day 1 (EoT Table 3-16). Most subjects had a peak in LSR for erythema, swelling, and vesiculation/pustulation at Day 5 and for crusting, flaking/scaling, and erosion/ulceration at Day 10 (Figure 12 and EoT Table 3-16).

Overall, the 4-day active treatment group had the highest maximal LSR scores for all individual LSR categories, followed by the 2-day- and 3-day active treatment groups that had similar maximal LSR scores, and the vehicle group had lowest maximal LSR scores (Figure 12, Table 47 and EoT Table 3-19). The trend was similar by country and no major differences in the individual LSR components were seen between the countries (EoT Table 3-18).
Table 47  Maximal local skin response score (LSR) post baseline by individual categories: safety analysis set

<table>
<thead>
<tr>
<th>Category</th>
<th>Maximal score</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
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<td>0.8</td>
</tr>
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<td></td>
<td>SD</td>
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<td>0.8</td>
<td>0.8</td>
<td>0.6</td>
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<tr>
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<td>Median</td>
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<td>3.0</td>
<td>3.0</td>
<td>1.0</td>
</tr>
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<td></td>
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<td>Number</td>
<td>55</td>
<td>59</td>
<td>48</td>
<td>59</td>
</tr>
<tr>
<td>Flaking/Scaling</td>
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<td>2.3</td>
<td>2.7</td>
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<td>0.8</td>
<td>0.7</td>
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<td>Number</td>
<td>55</td>
<td>59</td>
<td>48</td>
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</tr>
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<td>Number</td>
<td>55</td>
<td>59</td>
<td>48</td>
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Table 47  Maximal local skin response score (LSR) post baseline by individual categories: safety analysis set (continued)

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<th>Category</th>
<th>Maximal score</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
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<td>1.2</td>
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<td>48</td>
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</tr>
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<td>Maximum</td>
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<td>59</td>
<td>48</td>
<td>59</td>
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<td>59</td>
<td>48</td>
<td>59</td>
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10.3.3 Burning Sensation During Treatment

The subjects were asked to complete a Burning Sensation Diary on days 1 to 4, recording onset and duration of burning as well as the subject's feeling of burning using 5 descriptive categories: no burning, slightly burning, uncomfortable burning, very uncomfortable burning, and unbearable burning. A summary of burning sensation by day is presented in Table 48 and graphically in Figure 13.

The subjects in the 2-day, 3-day and vehicle treatment groups were treated with vehicle gel at Day 1 and most of these subjects had no burning at Day 1 (range 90.9% to 98.3%), whereas the majority of subjects in the 4-day active treatment group had burning (77.1%). In line with the treatment design the 4-day active treatment group had maximum burning sensation score at Day 1 and 2, the 2-day active treatment group had maximum scores at Day 3 and 4, and the 3-day active treatment group had increased scores at Day 2 with maximum scores at Day 3 and 4. Most subjects in the vehicle group had no burning sensation at any time point.

The maximum burning sensation was ‘unbearable burning’, recorded for 2 subjects in the 3-day active treatment group. The overall pattern of maximal burning was similar for the 2-day- and 3-day active treatment group and slightly higher for the 4-day active treatment group. No major differences were found in maximum burning sensation between Australia and the United States (Table 49).

The time from application to onset of burning sensation was generally between 2 and 5 hours for all active treatment groups (EoT Table 3-27).

Overall, the duration of all burning sensations at Day 1 to Day 4 was longer for the 4-day active treatment group than the 2-day- and 3-day active treatment group (EoT Table 3-28).

The correlation between maximal burning sensation and global satisfaction TSQM derived score was presented graphically in EoT Figure 3-6 and assessed by regression analysis in EoT Table 3-30. No statistically significant difference was seen for any of the active treatment groups (2-day: p=0.71; 3-day: p=0.71; 4-day: p=0.39), i.e. the burning sensation did not appear to reduce the treatment satisfaction. The global satisfaction TSQM derived score was compared with maximal duration of burning by 2 low levels of burning sensation (EoT Figure 3-7) and 2 high levels of burning sensation (EoT Figure 3-8). Regression analysis showed no statistically significant difference between the 2 high levels of burning sensation and TSQM for any of the active treatment groups (2-day: p=0.91; 3-day: p=0.089, 4-day: p=0.83) (EoT Table 3-31).
Figure 13  Plot burning category versus time by treatment group

% 100
90
80
70
60
50
40
30
20
10
0

1st active 2nd active 1st active 2nd active 3rd active 1st active 2nd active 3rd active 4th active

Ingenol 2 days

Ingenol 3 days

Ingenol 4 days

Cross-reference: EoT Figure 3-4
Table 48  Summary of burning sensation by day: safety analysis set

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<tr>
<th>Day</th>
<th>Burning sensation</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>n^i</td>
<td>%</td>
<td>n^i</td>
<td>%</td>
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<td>50</td>
<td>90.9</td>
<td>53</td>
<td>89.8</td>
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<tr>
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<td>Slight burning</td>
<td>4</td>
<td>7.3</td>
<td>6</td>
<td>10.2</td>
</tr>
<tr>
<td></td>
<td>Uncomfortable burning</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Very uncomfortable burning</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
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<td>55</td>
<td>100.0</td>
<td>59</td>
<td>100.0</td>
</tr>
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<td>No burning</td>
<td>49</td>
<td>89.1</td>
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<td>37.3</td>
</tr>
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<td>Slight burning</td>
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<td>9.1</td>
<td>22</td>
<td>37.3</td>
</tr>
<tr>
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<td>Uncomfortable burning</td>
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<td>1.8</td>
<td>11</td>
<td>18.6</td>
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<td>Very uncomfortable burning</td>
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<td>2</td>
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<td>Unbearable burning</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
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<td>100.0</td>
<td>59</td>
<td>100.0</td>
</tr>
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<td>27.3</td>
<td>15</td>
<td>26.3</td>
</tr>
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<td></td>
<td>Slight burning</td>
<td>33</td>
<td>60.0</td>
<td>29</td>
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<td>7.3</td>
<td>11</td>
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<td>Very uncomfortable burning</td>
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<td>5.5</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Unbearable burning</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>55</td>
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<td>57</td>
<td>100.0</td>
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</table>

24Nov14:08:31:01 LP0105 1020 t25 burn by day.doc Continued...
Table 48     Summary of burning sensation by day: safety analysis set (continued)

<table>
<thead>
<tr>
<th>Day</th>
<th>Burning sensation</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
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<tr>
<td>Day 4</td>
<td>No burning</td>
<td>17</td>
<td>30.9</td>
<td>19</td>
<td>34.5</td>
</tr>
<tr>
<td></td>
<td>Slight burning</td>
<td>26</td>
<td>47.3</td>
<td>28</td>
<td>50.9</td>
</tr>
<tr>
<td></td>
<td>Uncomfortable burning</td>
<td>9</td>
<td>16.4</td>
<td>5</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>Very uncomfortable burning</td>
<td>3</td>
<td>5.5</td>
<td>2</td>
<td>3.6</td>
</tr>
<tr>
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<td>1.8</td>
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<td>Total</td>
<td></td>
<td>55</td>
<td>100.0</td>
<td>55</td>
<td>100.0</td>
</tr>
</tbody>
</table>

1) n=Number of subjects

Cross-reference: EoT Table 3-26
<table>
<thead>
<tr>
<th>Maximal Burning</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>United States</td>
<td>Australia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No burning</td>
<td>No burning</td>
<td>No burning</td>
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</tr>
<tr>
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<td>Slight burning</td>
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<td>Slight burning</td>
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<td>Uncomfortable</td>
<td>Uncomfortable</td>
</tr>
<tr>
<td></td>
<td>Very uncomfortable</td>
<td>Very uncomfortable</td>
<td>Very uncomfortable</td>
<td>Very uncomfortable</td>
</tr>
<tr>
<td></td>
<td>Unbearable burning</td>
<td>Unbearable burning</td>
<td>Unbearable burning</td>
<td>Unbearable burning</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
</tr>
</tbody>
</table>

**Table 49**

Maximum burning sensation: safety analysis set

Ingenol 2 days (n=55) | Ingenol 3 days (n=59) | Ingenol 4 days (n=49) | Vehicle (n=61)

- **United States**
  - No burning: 4 (16.7%) 2 (7.7%) 2 (12.5%) 24 (96.0%)
  - Slight burning: 14 (58.3%) 15 (57.7%) 4 (25.0%) 1 (4.0%)
  - Uncomfortable burning:
    - Very uncomfortable: 3 (12.5%) 3 (11.5%) 2 (12.5%) 0 (0.0%)
    - Unbearable burning: 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
  - Total: 24 (100.0%) 26 (100.0%) 16 (100.0%) 25 (100.0%)

- **Australia**
  - No burning: 6 (19.4%) 5 (15.2%) 5 (15.6%) 33 (94.3%)
  - Slight burning: 16 (51.6%) 14 (42.4%) 8 (25.0%) 1 (2.9%)
  - Uncomfortable burning:
    - Very uncomfortable: 5 (16.1%) 12 (36.4%) 12 (37.5%) 1 (2.9%)
    - Unbearable burning: 4 (12.9%) 1 (3.0%) 7 (21.9%) 0 (0.0%)
  - Total: 31 (100.0%) 33 (100.0%) 32 (100.0%) 35 (100.0%)
Table 49  Maximum burning sensation: safety analysis set (continued)

<table>
<thead>
<tr>
<th>Maximal Burning</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>100.0</td>
<td>59</td>
<td>100.0</td>
</tr>
<tr>
<td>No burning</td>
<td>10</td>
<td>18.2</td>
<td>7</td>
<td>11.9</td>
</tr>
<tr>
<td>Slight burning</td>
<td>30</td>
<td>54.5</td>
<td>29</td>
<td>49.2</td>
</tr>
<tr>
<td>Uncomfortable burning</td>
<td>8</td>
<td>14.5</td>
<td>15</td>
<td>25.4</td>
</tr>
<tr>
<td>Very uncomfortable burning</td>
<td>7</td>
<td>12.7</td>
<td>4</td>
<td>6.8</td>
</tr>
<tr>
<td>Unbearable burning</td>
<td>0</td>
<td>0.0</td>
<td>4</td>
<td>6.8</td>
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<tr>
<td>Total</td>
<td>55</td>
<td>100.0</td>
<td>59</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Cross-reference: EoT Table 3-29
10.3.4 ECG Assessments - Change from Baseline to Visit 3

The ECG assessment was analysed by a central CRO and the results evaluation and conclusion is presented in a separate ECG Safety Report (Additional Related Reports).

Most subjects did not have post-dose emergent ECG abnormalities and there was no trend for an increase in the frequency of abnormal ECG values with increasing treatment duration (Additional Related Reports, Table 3). In conclusion, the results did not indicate an effect of ingenol mebutate on QTcF or on the other ECG intervals of interest (see Additional Related Reports).

10.3.5 Concomitant Medication and Concurrent Diagnoses During Trial

Concomitant Medication Inside Treatment Area Started During Trial

All treatment groups had subjects receiving concomitant medication inside the treatment area that started during the trial. The 4-day active treatment group had most subjects receiving concomitant medication (28.6%), followed by the 3-day active treatment group (23.7%), the 2-day active treatment group (14.5%), and the vehicle group (3.3%). The most common medications across all treatment groups were for the ATC index dermatologicals and various (other non-therapeutic axilliary products) (EoT Table 3-36).

All the applied concomitant medications are generally used in clinical practice for this type of population.

Concurrent Procedures Inside Treatment Area Started During Trial

All treatment groups had subjects with concurrent procedures inside the treatment area starting during the trial. The 3-day active treatment group had most subjects receiving concurrent procedures (8, 13.6%), followed by the 2-day- and 4-day active treatment groups (7 [12.7%] and 5 [10.2%], respectively), and the vehicle group (1, 1.6%) (EoT Table 3-37).

All the concurrent procedures are generally used in clinical practice for this type of population and no abnormal clinically significant procedures were found.

10.4 Clinical Laboratory Evaluation

Laboratory assessments were performed at Screening (Visit 1), Day 5 (Visit 3), and at Weeks 1 to 8 (Visit 4 to 7) until recovered for parameters outside the reference range. A listing of individual biochemistry and haematology laboratory values is presented in Appendix 2.8, Listing 8-1 and abnormal laboratory values are in Appendix 2.8, Listing 8-2.
Laboratory Values over Time

Overall, the haematology- and biochemistry laboratory parameters were similar at Baseline and Day 5 for all treatment groups. The mean level of C-reactive protein was slightly increased in the 3-day- and 4-day active treatment groups at Day 5 compared with Screening, which was expected as a reflection of the inflammation elicited by the treatment (EoT Tables 3-34 and 3-35).

Individual Clinically Significant Abnormalities

No clinically significant abnormalities relevant for the mostly elderly population in this trial were recorded in the haematology- or biochemistry laboratory parameters during the trial (Appendix 2.8, Listing 8-2).

10.5 Safety Conclusions

- The majority of the subjects in the active treatment groups had AEs and less than half of the subjects in the vehicle group had AEs (Section 10.1.2)

- Most subjects in the active treatment groups had AEs assessed as related to investigational product by the investigator (‘adverse drug reactions’). The 4-day active treatment group had highest percentage of subjects with related AEs (98.0%) followed by the 3-day-, 2-day-, and vehicle treatment groups (96.6%, 89.1%, and 16.4%, respectively) (Section 10.1.3)

- The most common AEs related to investigational product in all treatment groups were application site pain and application site pruritus. Most AEs related to the investigational product were recovered/resolved (Section 10.1.3)

- Most subjects in the active treatment groups had AEs in the treatment area: all subjects in the 4-day active treatment group, followed by the 3-day active treatment group (93.2%), and the 2-day active treatment group (89.1%) (Section 10.1.3)

- The most common AEs at the application site coded by LLT was application site burning and application site itching, of mostly mild or moderate severity (Section 10.1.3)

- The number of SAEs was similar in the active treatment groups with 3, 5, and 4 in the 2-day-, 3-day-, and 4-day active treatment groups, respectively. The most common SAE was SCC of skin (10 out of 12 events). No SAEs were reported for the vehicle group (Section 10.2)
• One AE lead to withdrawal from the trial (1 subject in the vehicle group). A total of 8 subjects discontinued treatment due to AEs: 1 subject in the 2-day active treatment group, 4 subjects in the 3-day active treatment group, 2 subjects in the 4-day active treatment group, and 1 subject in the vehicle group. The most common AE leading to discontinuation of treatment was application site pain (Section 10.2.3)

• The mean composite LSR score was highest at Day 5 in the 3-day- and 4-day active treatment groups and the 2-day active treatment group had highest composite LSR score at Day 5 and Day 10. The 4-day active treatment group had the highest mean composite LSR score at Day 5 (11.8), followed by the 3-day active treatment group (8.8), and the 2-day active treatment group (7.3). The vehicle group had similar score at all visits, corresponding to Baseline scores for the active treatment groups (Section 10.3.2.1)

• The active treatment groups had maximum burning sensation score ranging from the day of application of active treatment to 2 days after active treatment application. Most subjects in the vehicle group had no burning sensation at all time points. The overall pattern of maximal burning was similar for the 2-day- and 3-day active treatment group and slightly higher for the 4-day active treatment group (Section 10.3.3)

• ECG monitoring showed no association between ingenol mebutate treatment and evidence of cardiac effects (Section 10.3.4)

• Overall, the haematology- and biochemistry laboratory parameters were similar at Baseline and Day 5 for all treatment groups (Section 10.4)
11 Discussion and Overall Conclusions

11.1 Discussion

The primary objective of this trial was to evaluate efficacy of ingenol mebutate gel, 0.06% after once daily treatment for 2, 3 or 4 consecutive days compared to vehicle gel.

A total of 240 randomised subjects (i.e. 60 in each treatment group) were planned in the clinical study protocol (if all treatment groups continued after the 2 planned safety interim analyses) and 224 subjects were actually enrolled and randomised to treatment groups of similar size receiving either ingenol mebutate gel only, ingenol mebutate gel and vehicle gel, or vehicle gel only. The 4-day active treatment group was closed before completion of enrollment for the trial as an outcome of the final safety interim analysis and therefore comprised fewer subjects than the other treatment groups.

The majority of subjects (208 subjects, 92.9%) applied all 4 treatment doses with investigational product and the treatment compliance was similar for all treatment groups.

Most baseline demographic characteristics were balanced between the treatment groups and countries. However, mean duration of AK, mean composite LSR score, and mean AK lesion count was higher for Australia compared with the United States for all treatment groups. Most subjects were treated on the arm with or without back of hand, and the low number of subjects treated on the trunk or leg made results for these 2 locations difficult to interpret.

The trial population reflected the general population treated for AK, consisting of a majority of elderly men with fair skin and long duration of AKs. Most subjects (>90%) had previously been treated for AK and more than 75% of the subjects in all treatment groups had a history of non-melanoma skin cancer.

The primary endpoint was complete clearance of AKs at Week 8. A hierarchical order of statistical testing was applied which first tested the 3-day active treatment group and vehicle group, and, provided a significant test was found, allowed for testing of the 2-day active treatment group and vehicle group. The complete clearance was not statistically significantly different in the 3-day active treatment group (5.1%) vs. vehicle group (0.0%) (p=0.18).

The secondary endpoints were to evaluate reduction in AK count from Baseline to Week 8 and partial AK clearance at Week 8. Increased number of days of treatment with ingenol mebutate gel, 0.06% generally resulted in larger reduction of AK count and higher partial AK clearance. Hence, the 4-day-, 3-day- and 2-day regimens had lower mean AK count at Week 8 than vehicle (3.5, 4.0, 4.6, and 12.0 respectively) and higher partial AK clearance (60.4%, 56.2%, 47.3%, and 2.0%, respectively).
Due to the pre-defined order of testing and the lack of significance for the primary endpoint, no claims can be made for the secondary endpoints. However, the results for the secondary endpoints strongly and consistently supported the efficacy of the investigational product in the selected treatment area.

No safety concerns were identified for the 2-day- and 3-day active treatment groups in the trial. The 4-day active treatment group was closed as recommended by the DMC since pre-defined stopping criteria based on DLTs were met. Most subjects in the active treatment groups had AEs related to the investigational product and AEs that were present at the treatment site. The majority of these AEs were mild or moderate, and the occurrence of severe AEs were few and highest in the 4-day active treatment group and lowest in the 2-day active treatment group. The vehicle group had a lower number of AEs and no severe AEs. Few SAEs were reported and the number of SAEs was similar in the active treatment groups while no SAEs were reported for the vehicle group.

The most common AE in the trial was application site pain. As described in the Trial LP0105-1012 and the current trial, most of the application site pain events were coded as application site burning by LLT. The intensity of burning sensation was generally of mild to moderate intensity. According to the burning sensation diary the active treatment groups had maximum burning sensation score ranging from the day of application of active treatment to 2 days after active treatment application, the duration was generally between 2 and 5 hours, and the 4-day active treatment group had slightly higher score than the other active treatment groups. It should be noted that almost all subjects in all treatment groups received all applications of investigational product and that the treatment satisfaction according to the TSQM questionnaire was higher in all active treatment groups than the vehicle group. Thus the burning sensation seems to have been tolerable for most subjects, and was generally not seen as a reason to discontinue treatment.

SCC of skin was the most common AE in the second most common SOC ‘neoplasms, benign, malignant and unspecified (incl cysts and polyps)’. Inside the treatment area 11 AEs of SCC of skin, 2 keratoacanthomas, and 1 Bowen’s disease were diagnosed, almost exclusively in Australian subjects 1 month (median) after the treatment with ingenol mebutate gel 0.06% for 2, 3 or 4 days. The incidence of related SCCs was similar among the active treatment groups and the vehicle group did not have related SCCs. The subjects were at high risk of SCCs in that they had a high number of AKs at Baseline, a long history with AK, and almost all had a history of skin cancer. Thus, there is nothing surprising in the occurrence of SCCs in this population. The odd observation is that there were no cases in the vehicle group. This could be a statistical aberration; with around 60 patients the vehicle group could have a zero count without this being highly unlikely. In addition, AKs may progress to SCCs but the rate of
transformation from AKs to SCCs has been expected to occur during a longer period than the 8-week treatment period in the current trial (32). Thus, the progression of the SCCs in this trial most likely started before treatment with investigational product.

11.2 Overall Conclusions

Treatment in the 4-day active treatment group was closed early because trial-specific pre-defined stopping criteria for DLTs and other limiting events were met.

The trial did not show a statistically significant difference between active treatment (3-day regimen) and vehicle for the primary endpoint complete clearance of AKs at Week 8. However, the results for the secondary endpoints, reduction in AK count from baseline to Week 8 and partial clearance of AKs at Week 8 strongly and consistently supported the efficacy of ingenol mebutate gel, 0.06% for use in larger treatment areas (approximately 250 cm$^2$) of trunk and extremities. Acceptable tolerability was reported for the 2-day- and 3-day regimens.
12 References


26. Clinical Study Report. A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) gel, 0.015% in patients with actinic keratoses on the head (face or scalp) (REGION-IIa). Ballerup, LEO Pharma, Clinical Development, 08-Sep-2010. Study no.: PEP005-016.
27. Clinical Study Report. A multi-center, randomized, parallel group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) gel, 0.015% in patients with actinic keratoses on the head (face or scalp) (REGION-IIb). Ballerup, LEO Pharma, Clinical Development, 08-Sep-2010. Study no.: PEP005-025.

28. Clinical Study Report. A multi-centre, randomised, parallel group, double-blind, vehicle controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) Gel, 0.05% in patients with actinic keratosis on non-head locations (REGION-Ia). Ballerup, LEO Pharma, Clinical Development, 16-Sep-2010. Study no.: PEP005-014.

29. Clinical Study Report. A multi-centre, randomised, parallel group, double-blind, vehicle controlled study to evaluate the efficacy and safety of PEP005 (ingenol mebutate) gel, 0.05% in patients with actinic keratosis on non-head locations (REGION-Ib). Ballerup, LEO Pharma, Clinical Development, 08-Sep-2010. Study no.: PEP005-028.


13 Narratives

There are minor discrepancies in the details of the SAEs included in the clinical narratives compared with the patient data listings. This is because the data come from 2 different databases (i.e. locked clinical trial database and dynamic SAE safety database) and have been collected at different points in time. However, all key data points are reconciled. It is believed that these minor discrepancies do not change the overall clinical significance or understanding of the SAE.

13.1 Deaths

There were no deaths in this trial.

13.2 Other Serious Adverse Events

Subject No. **PPD** had an SAE (retinal melanoma) with onset at the clinical diagnosis date in the safety database and subject-expected onset date in the clinical database (2 months earlier). The event was non-treatment emergent in the clinical database as the subject-expected date of onset was 2 days prior to first application with investigational product. Hence, the total number of subjects with SAEs in the clinical database was 12, and 13 SAEs from the safety database are presented with narratives below. Please refer to Section 10.2.2 for an overview of the SAEs reported in the clinical database.

Subject Number: **PPD**; Angina Pectoris (Moderate)

This case concerns an **>80 year-old** subject diagnosed with AK. The subject was treated with vehicle gel once daily on **Day 1**, followed by ingenol mebutate gel 0.06% once daily from **Day 2** to **Day 4**. The subject received treatment for a total of 4 days and the last dose was applied on **Day 4**, according to protocol.

Medical history included history of **PPD** and **PPD** and **PPD** and **PPD**.

Concomitant medication included **PPD** and **PPD** and **PPD** and **PPD** and **PPD** and **PPD** and **PPD** and **PPD** and **PPD** and **PPD** and **PPD** and **PPD** and **PPD**.
The subject experienced moderate chest pain diagnosed as angina on Day 7, 7 days after first dose of investigational product and 4 days after last dose of investigational product, and was hospitalised. The chest pain was assessed as moderate by investigator.

On Day 8, the subject underwent angiogram which demonstrated mild coronary artery disease. The subject was discharged on Day 9 with new medications prescribed for medical management of coronary artery disease, included acetylsalicylic acid, amolodipine and nitroglycerin spray as needed. The subject remained well and was followed by a cardiologist.

The outcome of the event was reported as recovered with sequelae on Day 9.

Causality as per investigator: not related. Causality as per sponsor: not related.

Subject Number; Squamous Cell Carcinoma of Skin (Severe)

This case concerns a >70 year-old subject diagnosed with AK. Treatment with ingenol mebutate gel 0.06% once daily was started on Day 1. The subject received treatment on the right arm for a total of 4 days. The first dose was applied on Day 1 and the last dose was applied on Day 4.

Medical history included: from PPD to PPD; PPD of PPD and PPD; PPD; PPD; PPD; PPD; and PPD; PPD; PPD on PPD from PPD to PPD.

The subject did not receive relevant concomitant medications.

On Day 30, 29 days after first dose of investigational product, 3 lesions were noted on examination of the treatment area and all were thought to be keratoacanthomas. On Day 37, one of the lesions was identified by histopathological diagnosis as SCC of skin (see the summary below). The lesion was located on the application site, on right ulnar styloid and was assessed as severe by the investigator. The treatment for the SCC of skin was curettage.

The stop date of the event was reported as Day 60 and the event was reported as recovered.

Histopathology result summary:
Lesion 1: Right ulnar styloid – well differentiated squamoproliferative lesion
Lesion 2: Right ulnar styloid – well differentiated squamoproliferative lesion
Lesion 3: Right ulnar styloid – squamous cell carcinoma

Causality per investigator: possibly related. Causality per sponsor: possibly related.

Subject Number [PPD] Squamous Cell Carcinoma of Skin (Severe)

This case concerns an >80 year-old diagnosed with AK. The subject was treated with vehicle gel once daily from Day 1 to Day 2, followed by ingenol mebutate gel 0.06% once daily from Day 3 to Day 4, according to the protocol. The treatment was administered on the left forearm.

Medical history included [PPD] of [PPD] from [PPD], of [PPD] and [PPD] from [PPD], and [PPD].

Concomitant medications included [PPD] for [PPD], [PPD] for [PPD], [PPD] for [PPD], and [PPD].

Past medications used for the treatment of AK included cryo/liquid nitrogen and 5-fluorouracil.

The subject was clinically diagnosed with 2 SCCs Day 57, 56 days after first dose of investigational product. Both SCCs were on the left forearm in the treatment area. On Day 64 both SCCs were biopsied: excision biopsy specimen of skin from left mid forearm and punch biopsy specimen of skin from left lower forearm. The biopsies showed features of invasive SCC and were completely excised. On Day 64 a histopathological diagnosis confirmed the clinical diagnosis of SCC.
The stop date of the event was reported as **Day 78** and the outcome of the event was reported as recovered.

Causality as per investigator: possible. Causality as per sponsor: possible.

**Subject Number PPD; Squamous Cell Carcinoma of Skin (Mild)**

This case concerns a **70 year-old** diagnosed with AK. The subject was treated with vehicle gel once daily from **Day 1** to **Day 2**, followed by ingenol mebutate gel 0.06% once daily from **Day 3** to **Day 4**. The treatment was administered on arm excluding back of hand and the treatment with investigational product was completed according to protocol on **Day 4**.

Medical history included on nose on an unknown date in **April** to **May**, on nose on **July** from **August** to **September**, on nose on **September** from **October** to **November**, on nose on **November** from **December** to **January**, and on nose on **February** from **March** to **April**.

Concomitant medication included **PPD** for **PPD**, **PPD** for **PPD**, and the following for **PPD**: **PPD** with **PPD**, **PPD** with **PPD**, **PPD** with **PPD**, and **PPD**.

On Visit 6 (Day 31) the principle investigator noticed that there was a new lesion in the treated area and performed a punch biopsy on **Day 35**. On **Day 40**, 39 days after first dose of investigational product, the result of the histopathological diagnosis was digitate SCC in situ with cutaneous horn on sun damaged skin extending to the margins on left forearm. The subject was not hospitalised and the SCC was completely removed on **Day 71** as confirmed by laboratory analysis.

The outcome of the event was reported as recovered on **Day 71**, 32 days after the event start date.

Causality as per investigator: not related. Causality as per sponsor: not related.
Subject Number PPD; Squamous Cell Carcinoma of Skin (Severe)

This case concerns a >60 year-old diagnosed with AK. Treatment with ingenol mebutate gel 0.06% daily was started on Day 1 and the treatment area included the left arm. Treatment with investigational product was completed according to protocol on Day 4.

Medical history included PPD PPD PPD PPD PPD diagnosed at an unknown date before PPD and PPD PPD in PPD.

Concomitant medication included levothyroxine sodium for hypothyroidism.

The subject was clinically diagnosed with SCC Day 31, 31 days after first dose of investigational product. At a follow-up visit on Day 31 a biopsy was taken inside the treatment area of the lesion that had developed since Visit 5 (Day 17, PPD), and the event was assessed as severe by the investigator. On Day 33, the histopathological diagnosis of the biopsy revealed endophytic squamoproliferative lesion suspicious for invasive SCC. The lesion was fully excised on Day 39.

The outcome of the event was reported as recovered at time of report.

Causality as per investigator: probable. Causality as per sponsor: possible.

Subject Number PPD; Squamous Cell Carcinoma of Skin (Moderate)

This case concerns a <60 year-old diagnosed with AK. The subject was treated on the shin with vehicle gel once daily from Day 1 to Day 2, followed by ingenol mebutate gel 0.06% once daily from Day 3 to Day 4, according to protocol.

Medical history included PPD PPD PPD PPD PPD from PPD to PPD of PPD, PPD PPD PPD PPD PPD in PPD, PPD, PPD, PPD, PPD, PPD in PPD and PPD, PPD.

Concomitant medication included PPD for PPD PPD and PPD PPD PPD.

On Day 49, 48 days after first dose of investigational product the subject was clinically diagnosed with SCC in the treatment area (shin) and a biopsy was obtained. On Day 50, the biopsy was confirmed by histopathological diagnosis as SCC and was excised on PPD.

The outcome of the event was reported as recovered.
Causality as per investigator: possible. Causality as per sponsor: possible.

**Subject Number**: PPD; **Retinal Melanoma (Severe)**

This case concerns an >80 year-old diagnosed with AK. Treatment with ingenol mebutate 0.06% gel daily was started on **Day 1** and completed according to protocol on **Day 4**. The treatment was administered on right mid wrist.

Medical history included PPD in, PPD of, PPD on Day -29. Medical history included PPD in, PPD of, PPD on Day -27, PPD from, PPD from, PPD from, and PPD from.

No concomitant medication was reported.

The subject was diagnosed with retinal melanoma on the **Day 59**, 58 days after first dose of investigational product. On **Day 59**, retinal scan confirmed retinal melanoma. The subject had been having a visual disturbance of the left eye for the past 2 months, approximately since **Day -2**. On **Day 65**, the subject underwent surgery with enucleation of the left eye and insertion of an orbital implant. Also, on **Day 65**, the histology report confirmed a retinal melanoma with no evidence of transcleral spread. The following medications were used as part of the post-surgical treatment: intravenous fentanyl administered on **Day 65** for 1 day for pain, paracetamol 1 gram by mouth from **Day 65** to **Day 66** for pain and fever, and Tramadol 100 mg by mouth from **Day 65** for 1 day for pain.

At time of reporting, the subject had no left eye and would require a prosthesis.

The outcome of the event was reported as recovered with sequelae and the event stop date was reported as **Day 101**.

Causality as per investigator: not related. Causality as per sponsor: not related.

**Subject Number**: PPD; **Squamous Cell Carcinoma of Skin (Moderate)**

This case concerns a <80 year-old diagnosed with AK. The subject was treated with vehicle gel once daily on **Day 1**, followed by ingenol mebutate gel 0.06% once daily from **Day 2** to **Day 4**, according to protocol. The treatment area included the right forearm and dorsum of right hand.
Medical history included previous PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, and PPD.

Concomitant medication included PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, and PPD for PPD; PPD for PPD; PPD for PPD; and PPD PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, for PPD.

On Day 34, 33 days after first dose of investigational product, 2 SCCs were confirmed by clinical diagnosis in the treatment area (right forearm and dorsum of right hand) and the 2 carcinomas were excised the same day. Histopathological diagnosis confirmed the diagnosis of SCC in the treatment areas on the right forearm and right hand dorsum.

The outcome of the event was reported as recovered on Day 34.

Causality as per investigator: possible. Causality as per sponsor: possible.

Subject Number PPD; Squamous Cell Carcinoma of Skin (Moderate)

This case concerns a >70 year-old diagnosed with AK. The subject was treated with vehicle gel once daily on Day 1, followed by ingenol mebutate gel 0.06% once daily from Day 2 to Day 4, according to protocol. The investigational product was administered on the left wrist.

Medical history included PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, and PPD.

No relevant current medical conditions were reported.

Concomitant medication included PPD for PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, and PPD for PPD.

On Day 55, 54 days after first dose of investigational product, the subject was clinically diagnosed with SCC in the treatment area and the lesion was excised on Day 72. The result of the histopathological analysis of the biopsy revealed low grade Bowen’s disease and SCC.

The outcome of the event was reported as recovered/resolved on Day 72, 20 days after the start of the event.
Causality as per investigator: not related. Causality as per sponsor: not related.

**Subject Number PPD**: Squamous Cell Carcinoma of Skin (Mild)

This case concerns a >60 year-old diagnosed with AK. Treatment with ingenol mebutate gel 0.06% once daily topically, was started on Day 1 and completed according to protocol on Day 4. The treatment area was left forearm.

Medical history included PPD, PPD, and PPD. Concomitant medication included PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD, and PPD, PPD, PPD, PPD, PPD, PPD, PPD, PPD. All were ‘drug use for unknown indication’.

The subject had SCC in left inner forearm on Day 19 (Visit 4), 62 days after the first dose of investigational product: the subject had 2 early possible keratoacanthomas (superiorlateral) of approximately 3-4 mm in size, and was asked to contact the trial site if the size increased or if he developed symptoms. On Day 35 (Visit 5), the possible keratoacanthomas were still present and were to be biopsied if present at the final visit. On Day 85, a biopsy excision of skin of the left inner forearm was performed. On histopathological analysis confirmed SCC in the treatment area with hyperplastic keratosis with probable small area of invasive squamous cell.

The outcome of the event was reported as recovered.

Causality as per investigator: possible. Causality as per sponsor: possible.

**Subject Number PPD**: Keratoacanthoma (Moderate)

This case concerns a <70 year-old diagnosed with AK. Treatment with ingenol mebutate 0.06% gel once daily was started on Day 1 and completed according to protocol on Day 4. The treatment was administered on the right forearm.

Medical history included PPD, PPD, and PPD. Concomitant medication included PPD for PPD and PPD for PPD. On Day 26, 26 days after first dose of investigational product, the subject was diagnosed with keratoacanthoma carcinoma in the treatment area and it was present for approximately 4 weeks.
The outcome of the event was reported as recovered/resolved on Day 57.

No results from laboratory tests were reported.

Causality as per investigator: possible. Causality as per sponsor: possible.

**Subject Number PPD; Squamous Cell Carcinoma of Skin (Mild)**

This case concerns a >70 year-old diagnosed with AK. The subject was treated with vehicle gel once daily on Day 1, followed by ingenol mebutate gel 0.06% once daily from Day 2 to Day 4 according to protocol. The treatment was administered on the left arm.

Medical history included PPD, PPD, PPD, PPD, PPD, and PPD.

Concomitant medication included PPD, PPD, PPD, PPD, for PPD, PPD, PPD, and PPD, as needed for PPD, PPD, PPD, PPD, PPD, PPD, and PPD.

On Day 33 (Visit 6), 62 days after first dose of investigational product, 2 small lesions identified as possible AK or SCC were observed in the inferior treatment field. If they persisted they were to be biopsied. On Day 76, 1 lesion resided and curettage was performed. On Day 92, the histopathological diagnosis confirmed the finding of a SCC (low grade). The curettage was considered to be curative.

The outcome of the event was reported as recovered on Day 76.

Causality as per investigator: possible. Causality as per sponsor: possible.

**Subject Number PPD; Squamous Cell Carcinoma of Skin (Moderate)**

This case concerns a >60 year-old diagnosed with AK. The subject was treated with vehicle gel once daily on Day 1, followed by ingenol mebutate gel 0.06% once daily from Day 2 to Day 4, according to protocol. The treatment was administered on the right arm.

Medical history included PPD, PPD, PPD, PPD, PPD, and PPD.

Concomitant medication included PPD, PPD, PPD, PPD, for PPD, and PPD, PPD, for PPD.
On Day 54, 54 days after first dose of investigational product the subject had a biopsy performed of a suspicious lesion in the treatment area, and SCC was confirmed by histopathological analysis on Day 57. The lesion was excised on Day 78.

The outcome was reported as recovered.

Causality as per investigator: possible. Causality as per sponsor: possible.

### 13.3 Other Significant Adverse Events

**AEs leading to withdrawal from the trial**

One subject had an AE leading to withdrawal from the trial as described below.

**Subject PPD: Pneumonia (Moderate)**

This case concerns a <80 year-old diagnosed with AK. The subject was treated with vehicle gel once at Day 1. The treatment was administered on the arm and hand.

On Day 1 the subject withdrew from the trial due to pneumonia. The stop date of the event was Day 23.

The outcome of the event was recovered.

Causality as per investigator: not related.

**AEs leading to discontinued treatment**

Eight subjects had AEs leading to discontinued treatment, including subject PPD that was withdrawn from the trial. Narratives of the other 7 subjects are described below.

**Subject PPD: Application Site Pain and Eczema (both Moderate)**

This case concerns an >80 year-old diagnosed with AK. The subject was treated with vehicle gel once daily Day 1 to Day 2 followed by ingenol mebutate gel 0.06% once on Day 3. The treatment was administered on the arm excluding back of hand.

On Day 1 the subject had application site pain and on Day 3 the subject had eczema and discontinued treatment with investigational product. Application site pain was inside the treatment area and eczema was outside the treatment area. The stop date of the application site pain was Day 5 and eczema Day 16.

The outcome of both events was recovered.
Causality as per investigator: probably related for both events.

**Subject**<sup>PPD</sup>; Application Site Pain (Severe)

This case concerns a <60 year-old diagnosed with AK. The subject was treated with vehicle gel once on Day 1 followed by ingenol mebutate gel 0.06% once on Day 2. The treatment was administered on the arm and hand.

On Day 2 the subject had application site pain inside treatment area and discontinued treatment with investigational product. The stop date of the event was Day 12.

The outcome of the event was recovered.

Causality as per investigator: probably related.

**Subject**<sup>PPD</sup>; Application Site Pain (Severe), Application Site Hypersensitivity (Moderate), and Application Site Infection (Moderate)

This case concerns a <60 year-old diagnosed with AK. The subject was treated with vehicle gel once on Day 1 followed by ingenol mebutate gel 0.06% once on Day 2. The treatment was administered on the arm and hand.

On Day 3 the subject had application site pain, on Day 7 application site hypersensitivity, and on Day 8 application site infection, all inside the treatment area, and discontinued treatment with investigational product. The stop date was Day 16 for all events.

The outcome of the events was recovered.

Causality as per investigator: possibly related for application site infection, probably related for the other 2 events.

**Subject**<sup>PPD</sup>; Application Site Pain (Severe)

This case concerns a >70 year-old diagnosed with AK. The subject was treated with vehicle gel once on Day 1 followed by ingenol mebutate gel 0.06% once daily on Day 2 to Day 3. The treatment was administered on the arm and hand.

On Day 1 the subject had application site pain (burning) and application site pain (pain secondary to burning) inside the treatment area and discontinued treatment with investigational product. The stop date for both events was Day 6.
The outcome of both events was recovered.

Causality as per investigator: possibly related for both events.

Subject: Application Site Pain and Application Site Infection (Moderate)

This case concerns a >50 year-old diagnosed with AK. The subject was treated with vehicle gel once on Day 1 followed by ingenol mebutate gel 0.06% once on Day 2. The treatment was administered on the arm and hand.

On Day 2 and Day 3 the subject had application site pain (burning and pain, respectively) and on Day 8 application site infection in the treatment area and discontinued treatment with investigational product. The stop date was Day 4 for application site pain (burning), Day 15 for application site pain (pain), and Day 22 for application site infection.

The outcome of all events was recovered.

Causality as per investigator: possibly related for all events.

Subject: Application Site Pain (Severe)

This case concerns a >70 year-old diagnosed with AK. The subject was treated with ingenol mebutate gel 0.06% once daily at Day 1 to Day 3. The treatment was administered on the arm and hand.

On Day 1 the subject had application site pain and discontinued treatment with investigational product. The stop date was Day 8.

The outcome of the event was recovered.

Causality as per investigator: probably related.

Subject: Application Site Pain (Severe)

This case concerns a <70 year-old diagnosed with AK. The subject was treated with ingenol mebutate gel 0.06% once daily at Day 1 to Day 3. The treatment was administered on the arm and hand.

On Day 2 the subject had application site pain (burning heat), on Day 3 application site pain (pain) and discontinued treatment with investigational product. The stop date for both events was Day 6.
The outcome of both events was recovered.

Causality as per investigator: probably related for both events.
1 Tables and Figures, Baseline Characteristics and Investigational Product Data

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<table>
<thead>
<tr>
<th>Country</th>
<th>Centre</th>
<th>Total number of subjects enrolled (n=266)</th>
<th>Total number of subjects randomised (n=224)</th>
<th>Ingenol 2 days (n=55)</th>
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| **United States** |        |                                      |                                      |                 |                 |                 |               |
| PPD     | 9      | 8                                     | 2                                    | 2               | 2               | 2               | 2             |
| PPD     | 9      | 8                                     | 3                                    | 2               | 1               | 2               | 2             |
| PPD     | 2      | 1                                     | 0                                    | 0               | 1               | 0               | 0             |
| PPD     | 2      | 2                                     | 0                                    | 1               | 0               | 1               | 1             |
| PPD     | 11     | 7                                     | 1                                    | 3               | 1               | 2               | 1             |
| PPD     | 6      | 5                                     | 2                                    | 2               | 0               | 1               | 1             |
| PPD     | 20     | 8                                     | 2                                    | 2               | 1               | 3               | 3             |
| PPD     | 7      | 7                                     | 2                                    | 2               | 1               | 2               | 2             |
| PPD     | 5      | 4                                     | 1                                    | 1               | 1               | 1               | 1             |
| PPD     | 5      | 5                                     | 2                                    | 1               | 1               | 1               | 1             |
| PPD     | 22     | 22                                   | 5                                    | 6               | 5               | 6               | 6             |
| PPD     | 4      | 3                                     | 0                                    | 1               | 1               | 1               | 1             |
| PPD     | 4      | 3                                     | 1                                    | 1               | 0               | 1               | 1             |
| PPD     | 9      | 9                                     | 3                                    | 2               | 2               | 2               | 2             |
| **Total** |        | **266**                               | **224**                              | **55**          | **59**          | **49**          | **61**        |
### Table 1–2: Study period by country and centre: full analysis set

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Table 1–3: Reasons for withdrawal from trial: full analysis set

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¹) Subject thought he received Placebo and did not want to complete the trial
## Table 1–4: Anatomical treatment location by country and overall: full analysis set

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<th>Country/treatment location</th>
<th>All randomised subjects (n=224)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<tr>
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1) n=Number of subjects
Table 1–5: Number of AK lesions at baseline by country and overall: full analysis set

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Table 1–6: Number of AK lesions at baseline by analysis sites: full analysis set

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Table 1-6: Number of AK lesions at baseline by analysis sites: full analysis set (continued)

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Table 1-6: Number of AK lesions at baseline by analysis sites: full analysis set (continued)

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Table 1-6: Number of AK lesions at baseline by analysis sites: full analysis set (continued)

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Table 1–7: Number of AK lesions at baseline by anatomical location: full analysis set

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Table 1–8: Baseline composite LSR score by country and overall: safety analysis set

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## Table 1–9: Sex by country and overall: full analysis set

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<th>Vehicle (n=61)</th>
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<td>7 29.2</td>
<td>12 46.2</td>
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<td>26 100.0</td>
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<td>25 100.0</td>
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<td></td>
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<td>23 71.9</td>
<td>23 63.9</td>
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<tr>
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<td>15 45.5</td>
<td>9 28.1</td>
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<td>32 54.2</td>
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<td>49 100.0</td>
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Table 1–10: Skin type by country and overall: full analysis set

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<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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1) n=Number of subjects
Table 1–11: Race by country and overall: full analysis set

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<td>26 100.0</td>
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Table 1–12: Ethnic origin by country and overall: full analysis set

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1) n=Number of subjects
Table 1–13: Age by country and overall: full analysis set

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### Table 1–14: AK duration by country and overall: full analysis set

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Table 1–15: Vital signs at baseline: full analysis set

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Table 1-15: Vital signs at baseline: full analysis set (continued)

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Table 1–16: AK treatment history: full analysis set

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</tr>
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<td>12% lactic acid cream</td>
<td>0</td>
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<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>25% urea, 2% salicylic acid</td>
<td>0</td>
<td>0.0</td>
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<td>0.0</td>
</tr>
<tr>
<td>3% salicylic acid</td>
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<td>0</td>
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<tr>
<td>ALA 20%</td>
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<td>1</td>
<td>1.7</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Citra</td>
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<td>0.0</td>
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<td>1.7</td>
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<tr>
<td>Efudex</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Elocon ointment</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Elocon ointment and urea based</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Moisturiser</td>
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<td>Picato, scalp</td>
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</table>
Table 1-16: AK treatment history: full analysis set (continued)

<table>
<thead>
<tr>
<th>AK treatments</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Salicylic acid and urea emollient</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Urea cream</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Uroderm</td>
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<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Zyclara</td>
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<td>0.0</td>
</tr>
<tr>
<td>Total number of previous treatments</td>
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<td></td>
<td>143</td>
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<tr>
<td>Total number of previously treated subjects</td>
<td>54</td>
<td>98.2</td>
<td>55</td>
<td>93.2</td>
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1) n=Number of subjects
### Table 1-17: AK treatment history inside treatment area: full analysis set

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<th>AK treatments</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n¹</td>
<td>%</td>
<td>n¹</td>
<td>%</td>
</tr>
<tr>
<td>Cryo/Liquid nitrogen</td>
<td>31</td>
<td>56.4</td>
<td>29</td>
<td>49.2</td>
</tr>
<tr>
<td>Surgical excision/curettage</td>
<td>11</td>
<td>20.0</td>
<td>7</td>
<td>11.9</td>
</tr>
<tr>
<td>Dermabrasion</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Medium or greater depth chemical peel</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
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<tr>
<td>5-FLUOROURACIL</td>
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<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
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<tr>
<td>Photodynamic therapy</td>
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<td>5.5</td>
<td>4</td>
<td>6.8</td>
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<td>Retinoids</td>
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<td>12% lactic acid</td>
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<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Calmurid cream</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Effudex</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Elecon ointment and urea based moisturiser</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Lactic acid cream</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Salicylic acid</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Salicylic acid and urea emollient</td>
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<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Urea cream</td>
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<td>0.0</td>
</tr>
<tr>
<td><strong>Total number of previous treatments</strong></td>
<td>54</td>
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<td>45</td>
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<tr>
<td><strong>Total number of previously treated subjects</strong></td>
<td>33</td>
<td>60.0</td>
<td>30</td>
<td>50.8</td>
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</table>

1) n=Number of subjects
Table 1–18: Skin disease history: full analysis set

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Acanthoma</td>
<td>1</td>
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</tr>
<tr>
<td>Acrochordon</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Actinic keratosis</td>
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<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Anal cancer</td>
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<td>1.8</td>
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<td>0.0</td>
</tr>
<tr>
<td>Angiokeratoma</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Auricular perichondritis</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
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<td>61.8</td>
<td>34</td>
<td>57.6</td>
</tr>
<tr>
<td>Bowen's disease</td>
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<td>25.5</td>
<td>13</td>
<td>22.0</td>
</tr>
<tr>
<td>Brachioradial pruritus</td>
<td>0</td>
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<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Campbell de morgan spots</td>
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<td>0</td>
<td>0.0</td>
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<td>Cheilitis</td>
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<td>Cyst</td>
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<tr>
<td>Dermatitis contact</td>
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<td>1.8</td>
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</tr>
<tr>
<td>Dermatitis diaper</td>
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<tr>
<td>Dry skin</td>
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<td>1</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Table 1-18: Skin disease history: full analysis set (continued)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplastic naevus</td>
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<td>3</td>
<td>5.5</td>
<td>1</td>
</tr>
<tr>
<td>Eczema</td>
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<td>0.0</td>
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<td>Eczema nummular</td>
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<td>0</td>
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<td>Fibrous histiocytoma</td>
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<td>Haemangioma</td>
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<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Haemangioma of skin</td>
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<td>1</td>
<td>1.8</td>
<td>1</td>
</tr>
<tr>
<td>Hair follicle tumour benign</td>
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<td>1.8</td>
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<td>Herpes simplex</td>
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<td>Lentigo</td>
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<td>1.8</td>
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</tr>
<tr>
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<td>0.0</td>
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<td>Lichenoid keratosis</td>
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<td>0.0</td>
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</tr>
<tr>
<td>Malignant melanoma</td>
<td>5</td>
<td>5</td>
<td>9.1</td>
<td>7</td>
</tr>
<tr>
<td>Malignant melanoma in situ</td>
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<td>3</td>
<td>5.5</td>
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<td>Malignant melanoma stage II</td>
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<td>Melanocytic naevus</td>
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</tbody>
</table>
Table 1-18: Skin disease history: full analysis set (continued)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milia</td>
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<tr>
<td>Neurodermatitis</td>
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<td>Onychomycosis</td>
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</tr>
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<td>Oral herpes</td>
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<tr>
<td>Panniculitis</td>
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<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Photodermatosis</td>
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<td>0</td>
<td>0.0</td>
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</tr>
<tr>
<td>Pityriasis rosea</td>
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<td>Psoriasis</td>
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<td>Rosacea</td>
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<td>1.8</td>
<td>3</td>
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<td>Sarcoma of skin</td>
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<td>0</td>
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<td>Scar</td>
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<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Sebaceous hyperplasia</td>
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<td>1</td>
<td>1.8</td>
<td>2</td>
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<td>Seborrheic dermatitis</td>
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<td>1.8</td>
<td>5</td>
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<td>Seborrhoeic keratosis</td>
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<td>Skin cancer</td>
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<td>3</td>
<td>5.5</td>
<td>2</td>
</tr>
<tr>
<td>Skin papilloma</td>
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<td>1.8</td>
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</tr>
<tr>
<td>Skin wrinkling</td>
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<td>0</td>
<td>0.0</td>
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</tr>
</tbody>
</table>

Continued...
Table 1-18: Skin disease history: full analysis set (continued)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solar dermatitis</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Solar lentigo</td>
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<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
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<tr>
<td>Squamous cell carcinoma of skin</td>
<td>28</td>
<td>28</td>
<td>50.9</td>
<td>22</td>
</tr>
<tr>
<td>Stasis dermatitis</td>
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<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Telangiectasia</td>
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<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Tinea pedis</td>
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<td>1</td>
<td>1.8</td>
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</tr>
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<td>Transient acantholytic dermatosis</td>
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</tr>
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<td>Venous insufficiency</td>
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<tr>
<td>Vitiligo</td>
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<td>Xerosis</td>
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</tbody>
</table>

Total number of diagnoses: 123, 138, 124, 155
Total number of subjects: 50, 90.9, 49, 83.1, 41, 83.7, 52, 85.2

1) Classification according to MedDRA version 15.1
2) Different diagnoses within the same preferred term and involving the same subject have been counted as one. A subject could appear in multiple classes.
### Table 1–19: Skin disease history inside treatment area: full analysis set

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell carcinoma</td>
<td>5</td>
<td>5</td>
<td>9.1</td>
<td>3</td>
</tr>
<tr>
<td>Bowen's disease</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>2</td>
</tr>
<tr>
<td>Dry skin</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Haemangioma of skin</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Lentigo</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Photodermatitis</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Pityriasis rosea</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Seborrhoeic dermatitis</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Seborrhoeic keratosis</td>
<td>2</td>
<td>2</td>
<td>3.6</td>
<td>1</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Solar lentigo</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Squamous cell carcinoma of skin</td>
<td>2</td>
<td>2</td>
<td>3.6</td>
<td>1</td>
</tr>
<tr>
<td>Xerosis</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
</tbody>
</table>

Total number of diagnoses: 12, 15, 13, 9

Total number of subjects: 9, 16.4, 8, 13.6, 9, 18.4, 9, 14.8

---

1) Classification according to MedDRA version 15.1
2) Different diagnoses within the same preferred term and involving the same subject have been counted as one. A subject could appear in multiple classes.
Table 1–20: Protocol deviations leading to withdrawal from per protocol analysis set: full analysis set

<table>
<thead>
<tr>
<th>Protocol deviation</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Premature withdrawal</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Did not apply full dose</td>
<td>1</td>
<td>1.8</td>
<td>6</td>
<td>10.2</td>
</tr>
<tr>
<td>Disallowed medication used</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Biopsy within STA</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>3</td>
<td>5.5</td>
<td>8</td>
<td>13.6</td>
</tr>
</tbody>
</table>
Table 1–21: Concomitant medications at baseline: full analysis set

<table>
<thead>
<tr>
<th>ATC classification index level 1</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Drugs</td>
<td>No. Subj</td>
<td>%</td>
<td>No. Drugs</td>
</tr>
<tr>
<td>Alimentary tract and metabolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>35</td>
<td>63.6</td>
<td>60</td>
</tr>
<tr>
<td>Antiinfectives for systemic use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5</td>
<td>9.1</td>
<td>0</td>
</tr>
<tr>
<td>Antineoplastic and immunomodulating agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and blood forming organs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>15</td>
<td>27.3</td>
<td>29</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>92</td>
<td>40</td>
<td>72.7</td>
<td>87</td>
</tr>
<tr>
<td>Dermatologicals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>9</td>
<td>16.4</td>
<td>5</td>
</tr>
<tr>
<td>Genito urinary system and sex hormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>11</td>
<td>20.0</td>
<td>9</td>
</tr>
<tr>
<td>Musculo-Skeletal system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>16</td>
<td>29.1</td>
<td>16</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>18</td>
<td>32.7</td>
<td>31</td>
</tr>
<tr>
<td>Respiratory system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>10</td>
<td>18.2</td>
<td>26</td>
</tr>
<tr>
<td>Sensory organs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>4</td>
<td>7.3</td>
<td>0</td>
</tr>
<tr>
<td>Systemic hormonal preparations, excl. sex hormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6</td>
<td>10.9</td>
<td>4</td>
</tr>
<tr>
<td>Various</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>7</td>
<td>12.7</td>
<td>3</td>
</tr>
</tbody>
</table>

Total number of drugs taken: 293

Total number of subjects taking drugs: 53

1) Drugs with the same Anatomical Therapeutic Chemical (ATC) classification level 4 code and generic name/preferred term name which have been taken by the same subject have been counted as one.
**Table 1–22: Concurrent diagnoses at baseline by medDRA Primary System Organ Class (SOC): full analysis set**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>6 2 3.6</td>
<td>2 2 3.4</td>
<td>0 0 0.0</td>
<td>2 2 3.3</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>11 9 16.4</td>
<td>19 13 22.0</td>
<td>13 8 16.3</td>
<td>24 16 26.2</td>
</tr>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td>1 1 1.8</td>
<td>0 0 0.0</td>
<td>0 0 0.0</td>
<td>1 1 1.6</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>1 1 1.8</td>
<td>1 1 1.7</td>
<td>5 5 10.2</td>
<td>2 2 3.3</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>6 6 10.9</td>
<td>4 4 6.8</td>
<td>2 2 4.1</td>
<td>4 4 6.6</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>6 6 10.9</td>
<td>3 3 5.1</td>
<td>4 2 4.1</td>
<td>7 7 11.5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>24 20 36.4</td>
<td>16 13 22.0</td>
<td>22 15 30.6</td>
<td>26 22 36.1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>8 7 12.7</td>
<td>3 3 5.1</td>
<td>2 2 4.1</td>
<td>3 2 3.3</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>1 1 1.8</td>
<td>0 0 0.0</td>
<td>2 2 4.1</td>
<td>1 1 1.6</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>11 10 18.2</td>
<td>10 9 15.3</td>
<td>11 10 20.4</td>
<td>11 10 16.4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>8 7 12.7</td>
<td>4 4 6.8</td>
<td>3 3 6.1</td>
<td>5 5 8.2</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>2 2 3.6</td>
<td>0 0 0.0</td>
<td>1 1 2.0</td>
<td>1 1 1.6</td>
</tr>
<tr>
<td>Investigations</td>
<td>13 12 21.8</td>
<td>7 5 8.5</td>
<td>9 7 14.3</td>
<td>16 9 14.8</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>36 25 45.5</td>
<td>33 23 39.0</td>
<td>28 22 44.9</td>
<td>56 36 59.0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>25 19 34.5</td>
<td>30 23 39.0</td>
<td>19 16 32.7</td>
<td>24 19 31.1</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>8 1 1.8</td>
<td>11 4 6.8</td>
<td>9 4 8.2</td>
<td>7 1 1.6</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3 3 5.5</td>
<td>12 12 20.3</td>
<td>6 4 8.2</td>
<td>15 13 21.3</td>
</tr>
</tbody>
</table>

30.JUN15:11:48:43 LP0105 1020 t22 condiag.doc Continued...
Table 1-22: Concurrent diagnoses at baseline by medDRA Primary System Organ Class (SOC): full analysis set (continued)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>13</td>
<td>9</td>
<td>16.4</td>
<td>12</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3</td>
<td>3</td>
<td>5.5</td>
<td>6</td>
</tr>
<tr>
<td>Reproductive system and breast</td>
<td>5</td>
<td>5</td>
<td>9.1</td>
<td>8</td>
</tr>
<tr>
<td>disorders</td>
<td>7</td>
<td>7</td>
<td>12.7</td>
<td>17</td>
</tr>
<tr>
<td>Respiratory, thoracic and</td>
<td>16</td>
<td>9</td>
<td>16.4</td>
<td>5</td>
</tr>
<tr>
<td>mediastinal disorders</td>
<td>4</td>
<td>4</td>
<td>7.3</td>
<td>4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>43</td>
<td>31</td>
<td>56.4</td>
<td>39</td>
</tr>
<tr>
<td>disorders</td>
<td>30</td>
<td>30</td>
<td>54.5</td>
<td>29</td>
</tr>
<tr>
<td>Total number of diagnoses</td>
<td>291</td>
<td></td>
<td></td>
<td>275</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>48</td>
<td>87.3</td>
<td>45</td>
<td>76.3</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1
2) Different diagnoses within the same preferred term and involving the same subject have been counted as one. A subject could appear in multiple classes.
Table 1–23: Number of treatment doses applied: safety analysis set

<table>
<thead>
<tr>
<th>Number of treatment doses</th>
<th>All randomised subjects (n=224)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
</tr>
<tr>
<td>1</td>
<td>3 1.3</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>1 2.0</td>
<td>2 3.3</td>
</tr>
<tr>
<td>2</td>
<td>3 1.3</td>
<td>0 0.0</td>
<td>3 5.1</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>3</td>
<td>10 4.5</td>
<td>1 1.8</td>
<td>2 3.4</td>
<td>5 10.2</td>
<td>2 3.3</td>
</tr>
<tr>
<td>4</td>
<td>208 92.9</td>
<td>54 98.2</td>
<td>54 91.5</td>
<td>43 87.8</td>
<td>57 93.4</td>
</tr>
<tr>
<td>Total</td>
<td>224 100.0</td>
<td>55 100.0</td>
<td>59 100.0</td>
<td>49 100.0</td>
<td>61 100.0</td>
</tr>
</tbody>
</table>

1) Subject (3-day active group) applied 4 doses but in 5 days as the first dose was partly used on day 1 and partly used on day 2, second dose on day 3, third dose on day 4 and fourth dose on day 5.
### Table 1–24: Non-melanoma skin cancer history: full analysis set

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell carcinoma</td>
<td>35</td>
<td>35</td>
<td>63.6</td>
<td>36</td>
</tr>
<tr>
<td>Bowen's disease</td>
<td>14</td>
<td>14</td>
<td>25.5</td>
<td>13</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>3</td>
<td>3</td>
<td>5.5</td>
<td>2</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Squamous cell carcinoma of skin</td>
<td>28</td>
<td>28</td>
<td>50.9</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total number of diagnoses</strong></td>
<td></td>
<td></td>
<td></td>
<td>80</td>
</tr>
<tr>
<td><strong>Total number of subjects</strong></td>
<td>46</td>
<td>83.6</td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1
2) Different diagnoses within the same preferred term and involving the same subject have been counted as one. A subject could appear in multiple classes.
Figure 1-1: Subject disposition

Vehicle

- 61
- 59
- 58
- 57
- 57
- 58

1 AE, 1 other
1 lost to follow-up

Ingenol 4 days

- 49
- 48
- 48
- 47
- 48
- 48

1 voluntary

Ingenol 3 days

- 59
- 59
- 59
- 59
- 58
- 58

1 lost to follow-up

Ingenol 2 days

- 55
- 55
- 55
- 55
- 54
- 55

All subjects

- 266
- 224
- 221
- 220
- 218
- 217
- 219

Enrolment
Visit 1
Randomisation
Visit 2/ Day 1
Visit 3/ Day 5
Visit 4/ Day 10
Visit 5/ Day 17
Visit 6/ Day 31
Visit 7/ Day 56
Figure 1-2: Analysis datasets

Enrolled: 266

Randomised: 224
- 55: Ingenol 2 days
- 59: Ingenol 3 days
- 49: Ingenol 4 days
- 61: Vehicle

Safety analysis set: 224
- 55: Ingenol 2 days
- 59: Ingenol 3 days
- 49: Ingenol 4 days
- 61: Vehicle

Per protocol analysis set: 196
- 52: Ingenol 2 days
- 51: Ingenol 3 days
- 38: Ingenol 4 days
- 55: Vehicle
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Table 2–1: Complete clearance of AK 8 weeks after treatment (multiple imputation): full analysis set

<table>
<thead>
<tr>
<th>Complete clearance at 8 weeks</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>N¹</td>
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1) n/1000 from 1000 imputations of AK count at week 8 using a negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset.
Table 2–2: Complete clearance of AK 8 weeks after treatment (observed case): full analysis set

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<th></th>
<th>Vehicle (n=61)</th>
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<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
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Table 2–3: Complete clearance of AK 8 weeks after treatment (worst case scenario): full analysis set

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<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>%</td>
<td>Number of subjects</td>
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Table 2–4: Primary statistical analysis of complete clearance of AK 8 weeks after treatment (multiple imputation): full analysis set

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<th>Treatment comparison</th>
<th>Relative risk [95% CI]</th>
<th>P-value</th>
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<tbody>
<tr>
<td>a) Ingenol 3 days versus Vehicle</td>
<td>2.97 [0.60 to 14.74]</td>
<td>0.18</td>
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<tr>
<td>b) Ingenol 2 days versus Vehicle</td>
<td>3.51 [1.00 to 12.41]</td>
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<tr>
<td>c) Ingenol 3 days versus Ingenol 2 days</td>
<td>0.47 [0.13 to 1.68]</td>
<td>0.25</td>
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1) Based on 1000 imputations of AK count at week 8 using a negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset
2) Adjusted for analysis site using Rubin’s pooling methodology after log transformation of RR of each imputation. Complete clearance relative to vehicle group (a and b) and 2-day group (c)
3) CMH logit estimators were used for comparisons with vehicle due to absence of cleared subject in the vehicle group
4) Type I error not controlled
5) Mantel-Haenszel estimators
Table 2–5: Statistical analysis of complete clearance of AK 8 weeks after treatment (observed case): full analysis set

<table>
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<tr>
<th>Treatment comparison</th>
<th>Relative risk [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Global General association</td>
<td>1</td>
<td>P=0.025</td>
</tr>
<tr>
<td>b) Ingenol 3 days versus Vehicle</td>
<td>2.60 [0.54 to 12.58]</td>
<td>P=0.12</td>
</tr>
<tr>
<td>c) Ingenol 2 days versus Vehicle</td>
<td>3.54 [1.01 to 12.47]</td>
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<td>d) Ingenol 3 days versus 2 days</td>
<td>0.47 [0.13 to 1.67]</td>
<td>P=0.22</td>
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</table>

1) Adjusted for analysis site. Relative risk of complete clearance relative to vehicle group (b and c) and 2-day group (d).
2) CMH logit estimators were used for comparisons with vehicle due to absence of cleared subject in the vehicle group.
3) Type I error not controlled.
4) Mantel-Haenszel estimators.
5) P-value from Fishers Exact Test b)=0.24, c)=0.005, d)=0.20.
Table 2–6: Statistical analysis of complete clearance of AK 8 weeks after treatment (worst case scenario): full analysis set

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<th>Treatment comparison</th>
<th>Relative risk [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
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<td>1.0</td>
<td>0.29</td>
</tr>
<tr>
<td>b) Ingenol 3 days versus Vehicle</td>
<td>1.15 [0.24 to 5.47]</td>
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<td>c) Ingenol 2 days versus Vehicle</td>
<td>2.53 [0.64 to 10.01]</td>
<td>0.16</td>
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<tr>
<td>d) Ingenol 3 days versus 2 days</td>
<td>0.47 [0.13 to 1.67]</td>
<td>0.22</td>
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1) Adjusted for analysis site with Mantel-Haenszel estimators.
   Relative risk of complete clearance relative to vehicle group (b and c) and 2-day group d)
2) Type I error not controlled
3) P-value from Fishers Exact Test b)=1.0, c)=0.19, d)=0.19
Table 2-7: Complete clearance of AK by visit (observed case): full analysis set

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<th>Visit Complete clearance</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
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</tr>
<tr>
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Table 2–8: Complete clearance of AK 8 weeks after treatment by analysis site (observed case): full analysis set

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<tr>
<th>Site</th>
<th>Complete clearance</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
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<tr>
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<td></td>
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<td>%</td>
<td>%</td>
<td>%</td>
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</tr>
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Table 2-8: Complete clearance of AK 8 weeks after treatment by analysis site (observed case): full analysis set (continued)

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<th>Site</th>
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<th>Ingenol 2 days (n=55)</th>
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<th>Ingenol 4 days (n=49)</th>
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Table 2-8: Complete clearance of AK 8 weeks after treatment by analysis site (observed case): full analysis set (continued)

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<th>Complete clearance</th>
<th>Ingenol 2 days (n=55)</th>
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Table 2-8: Complete clearance of AK 8 weeks after treatment by analysis site (observed case): full analysis set (continued)

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<th>Site</th>
<th>Complete clearance</th>
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<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
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Table 2–9: Complete clearance of AK 8 weeks after treatment by anatomical location (observed case): full analysis set

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<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
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Table 2–10: Complete clearance of AK 8 weeks after treatment by country (observed case): full analysis set

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<th>Country</th>
<th>Complete clearance</th>
<th>Ingenol 2 days (n=55)</th>
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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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Table 2–11: Complete clearance of AK 8 weeks after treatment: per protocol analysis set

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<th>Complete clearance at 8 weeks</th>
<th>Ingenol 2 days (n=52)</th>
<th>Ingenol 3 days (n=51)</th>
<th>Ingenol 4 days (n=38)</th>
<th>Vehicle (n=55)</th>
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<td>Number of subjects</td>
<td>Number of subjects</td>
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<td></td>
<td>13.5%</td>
<td>3.9%</td>
<td>26.3%</td>
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<td>49</td>
<td>28</td>
<td>55</td>
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<tr>
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<td>86.5%</td>
<td>96.1%</td>
<td>73.7%</td>
<td>100.0%</td>
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<td>51</td>
<td>38</td>
<td>55</td>
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<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
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Table 2–12: Statistical analysis of complete clearance of AK 8 weeks after treatment: per protocol analysis set

<table>
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<tr>
<th>Treatment comparison</th>
<th>Relative risk [95% CI]</th>
<th>P-value</th>
</tr>
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<tr>
<td>a) Global General association</td>
<td>2.43 [0.36 to 16.51]</td>
<td>P=0.025</td>
</tr>
<tr>
<td>b) Ingenol 3 days versus Vehicle</td>
<td>3.21 [0.92 to 11.16]</td>
<td>P=0.008</td>
</tr>
<tr>
<td>c) Ingenol 2 days versus Vehicle</td>
<td>0.35 [0.08 to 1.51]</td>
<td>P=0.13</td>
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<tr>
<td>d) Ingenol 3 days versus 2 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) Adjusted for analysis site. Relative risk of complete clearance relative to vehicle group (b and c) and 2-day group (d)
2) CMH logit estimators were used for comparisons with vehicle due to absence of cleared subject in the vehicle group
3) Type I error not controlled
4) Mantel-Haenszel estimators
5) P-value from Fishers Exact Test b)=0.23, c)=0.005, d)=0.16
Table 2–13: Reduction in AK count 8 weeks after treatment (multiple imputation): full analysis set

<table>
<thead>
<tr>
<th>AK count</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed mean(^1)</td>
<td>4.6</td>
<td>4.0</td>
<td>3.5</td>
<td>12.0</td>
</tr>
<tr>
<td>Adjusted(^1) mean</td>
<td>4.0</td>
<td>3.6</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Adjusted(^2) percentage reduction from baseline</td>
<td>64.5</td>
<td>68.3</td>
<td>11.9</td>
<td></td>
</tr>
</tbody>
</table>

1) Based on 1000 imputations of AK count at week 8 using a negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset
2) From negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset
Table 2–14: Reduction in AK count 8 weeks after treatment (observed case): full analysis set

<table>
<thead>
<tr>
<th>AK count</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed mean</td>
<td>4.6</td>
<td>3.9</td>
<td>3.5</td>
<td>11.0</td>
</tr>
<tr>
<td>Adjusted mean</td>
<td>4.0</td>
<td>3.5</td>
<td>3.5</td>
<td>9.8</td>
</tr>
<tr>
<td>Adjusted percentage reduction from baseline</td>
<td>64.6</td>
<td>68.8</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>Lower 95% CI</td>
<td>58.1</td>
<td>63.1</td>
<td>1.4</td>
<td>23.8</td>
</tr>
<tr>
<td>Upper 95% CI</td>
<td>70.1</td>
<td>73.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) From negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset
Table 2–15: Reduction in AK count 8 weeks after treatment (worst case scenario): full analysis set

<table>
<thead>
<tr>
<th>AK count</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed mean</td>
<td>4.6</td>
<td>4.2</td>
<td>3.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Adjusted(^1) mean</td>
<td>4.0</td>
<td>3.7</td>
<td></td>
<td>9.4</td>
</tr>
<tr>
<td>Adjusted(^1) percentage reduction from baseline</td>
<td>64.5</td>
<td>67.5</td>
<td></td>
<td>17.3</td>
</tr>
<tr>
<td>Lower 95% CI</td>
<td>57.1</td>
<td>61.0</td>
<td>4.1</td>
<td>28.7</td>
</tr>
<tr>
<td>Upper 95% CI</td>
<td>70.5</td>
<td>72.9</td>
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</tr>
</tbody>
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1) From negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset
Table 2–16: Statistical analysis of AK count 8 weeks after treatment (multiple imputation): full analysis set

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>Ratio of adjusted means(^1)</th>
<th>[95% CI](^1)</th>
<th>P-value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ingenol 2 days versus Vehicle</td>
<td>0.40</td>
<td>[ 0.32 to 0.51]</td>
<td>P=(&lt; 0.001</td>
</tr>
<tr>
<td>b) Ingenol 3 days versus Vehicle</td>
<td>0.36</td>
<td>[ 0.29 to 0.45]</td>
<td>P=(&lt; 0.001</td>
</tr>
<tr>
<td>c) Ingenol 3 days versus Ingenol 2 days</td>
<td>0.89</td>
<td>[ 0.70 to 1.14]</td>
<td>P=0.36</td>
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\(^1\) From negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset with 1000 imputations.
### Table 2–17: Statistical analysis of AK count 8 weeks after treatment (observed case): full analysis set

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>Ratio of adjusted means$^1$</th>
<th>[95% CI]$^1$</th>
<th>P-value$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ingenol 3 days versus Vehicle</td>
<td>0.36</td>
<td>[0.29 to 0.45]</td>
<td>P&lt;$&lt; 0.001$</td>
</tr>
<tr>
<td>b) Ingenol 2 days versus Vehicle</td>
<td>0.41</td>
<td>[0.33 to 0.51]</td>
<td>P&lt;$&lt; 0.001$</td>
</tr>
<tr>
<td>c) Ingenol 3 days versus Ingenol 2 days</td>
<td>0.88</td>
<td>[0.70 to 1.12]</td>
<td>P$= 0.30$</td>
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1) From negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset.
Table 2–18: Statistical analysis of AK count 8 weeks after treatment (worst case scenario): full analysis set

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>Ratio of adjusted means(^1)</th>
<th>[95% CI](^1)</th>
<th>P-value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ingenol 3 days versus Vehicle</td>
<td>0.39</td>
<td>[ 0.31 to 0.50]</td>
<td>P&lt; 0.001</td>
</tr>
<tr>
<td>b) Ingenol 2 days versus Vehicle</td>
<td>0.43</td>
<td>[ 0.34 to 0.55]</td>
<td>P&lt; 0.001</td>
</tr>
<tr>
<td>c) Ingenol 3 days versus Ingenol 2 days</td>
<td>0.91</td>
<td>[ 0.70 to 1.19]</td>
<td>P= 0.50</td>
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1) From negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset.
Table 2–19: Reduction in AK count by visit (observed case): full analysis set

<table>
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<tr>
<th>Visit</th>
<th>%Change in AK count</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<tbody>
<tr>
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<td>29.8</td>
<td>27.5</td>
<td>25.3</td>
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<tr>
<td></td>
<td>Median</td>
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<td>-100.0</td>
<td>-100.0</td>
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<td>Day 56</td>
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Table 2–20: Reduction in AK count 8 weeks after treatment by analysis site (observed case): full analysis set

<table>
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<th>Site</th>
<th>%Change in AK count</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
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Table 2-21: Reduction in AK count 8 weeks after treatment by anatomical location (observed case): full analysis set (continued)

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<th>Ingenol 2 days (n=55)</th>
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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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Table 2–22: Reduction in AK count 8 weeks after treatment by country (observed case):
full analysis set

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<th>Vehicle (n=61)</th>
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Table 2–23: Partial clearance of AK 8 weeks after treatment (multiple imputation): full analysis set

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<th>Partial clearance at 8 weeks</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
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<tr>
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<td>N¹  %</td>
<td>N¹  %</td>
<td>N¹  %</td>
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<td>29.6  60.4</td>
<td>1.2  2.0</td>
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<td>25.9  43.8</td>
<td>19.4  39.6</td>
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</table>

1) n/1000 from 1000 imputations of AK count at week 8 using a negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset
Table 2–24: Partial clearance of AK 8 weeks after treatment (observed case): full analysis set

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<th>Partial clearance at 8 weeks</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
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<td>%</td>
<td>Number of subjects</td>
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Table 2-25: partial clearance of AK 8 weeks after treatment (worst case scenario): full analysis set

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<th>Partial clearance at 8 weeks</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>%</td>
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<td>44.1</td>
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Table 2–26: Statistical analysis of partial clearance of AK 8 weeks after treatment (multiple imputation): full analysis set

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>Relative risk [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ingenol 3 days versus Vehicle</td>
<td>32.26 [ 4.39 to 236.8]</td>
<td>P&lt; 0.001</td>
</tr>
<tr>
<td>b) Ingenol 2 days versus Vehicle</td>
<td>25.20 [ 3.39 to 187.4]</td>
<td>P=0.002</td>
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<td>c) Ingenol 3 days versus Ingenol 2 days</td>
<td>1.20 [ 0.86 to 1.65]</td>
<td>P=0.28</td>
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</table>

1) Based on 1000 imputations of AK count at week 8 using a negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset.
2) Adjusted for analysis site. Relative risk of partial clearance relative to vehicle group (a and b) and 2-day group (c).
3) Mantel-Haenszel estimators.
Table 2–27: Statistical analysis of partial clearance of AK 8 weeks after treatment (observed case): full analysis set

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>Relative risk* • [95% CI]*</th>
<th>P-value*</th>
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</thead>
<tbody>
<tr>
<td>a) Global General association</td>
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<tr>
<td>b) Ingenol 3 days versus Vehicle</td>
<td>36.13 [4.77 to 273.5]</td>
<td>P=&lt; 0.001</td>
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<td>c) Ingenol 2 days versus Vehicle</td>
<td>28.37 [3.71 to 217.1]</td>
<td>P=&lt; 0.001</td>
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<tr>
<td>d) Ingenol 3 days versus 2 days</td>
<td>1.21 [0.87 to 1.67]</td>
<td>P=0.27</td>
</tr>
</tbody>
</table>

1) Adjusted for analysis site. Relative risk of partial clearance relative to vehicle group (b and c) and 2-day group (d)
2) Mantel-Haenszel estimators
Table 2–28: Statistical analysis of partial clearance of AK 8 weeks after treatment (worst case scenario): full analysis set

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<tr>
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<th>Relative risk*</th>
<th>[95% CI]*</th>
<th>P-value</th>
</tr>
</thead>
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<td>b) Ingenol 3 days versus Vehicle</td>
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<td>[2.55 to 19.79]</td>
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<td>[0.86 to 1.65]</td>
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<td>d) Ingenol 3 days versus 2 days</td>
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1) Adjusted for analysis site. Relative risk of partial clearance relative to vehicle group (b and c) and 2-day group (d)
2) Mantel-Haenszel estimators
Table 2–29: Partial clearance of AK by visit (observed case): full analysis set

<table>
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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>%</td>
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Table 2–30: Partial clearance of AK 8 weeks after treatment by analysis site (observed case): full analysis set

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<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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Table 2-30: Partial clearance of AK 8 weeks after treatment by analysis site (observed case): full analysis set (continued)

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Table 2-30: Partial clearance of AK 8 weeks after treatment by analysis site (observed case): full analysis set (continued)

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<th>Partial clearance</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
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<td>3 100.0</td>
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Table 2-30: Partial clearance of AK 8 weeks after treatment by analysis site (observed case): full analysis set (continued)

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<th>%</th>
<th>%</th>
<th>%</th>
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<td>(n=49)</td>
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<td>19</td>
<td>19</td>
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<td>100.0</td>
<td>100.0</td>
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</table>
Table 2–31: Partial clearance of AK 8 weeks after treatment by anatomical location (observed case): full analysis set

| Location                        | Partial clearance | Ingenol 2 days  
<table>
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<tr>
<th></th>
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<th>Number of subjects</th>
<th>(n=59)</th>
<th>Number of subjects</th>
<th>(n=49)</th>
<th>Number of subjects</th>
<th>(n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm including back of hand</td>
<td>Yes</td>
<td>15</td>
<td>46.9</td>
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<td>56.7</td>
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<td>53.6</td>
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<tr>
<td>No</td>
<td>17</td>
<td>53.1</td>
<td>13</td>
<td>43.3</td>
<td>13</td>
<td>46.4</td>
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<td>24</td>
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<td>11</td>
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<td>71.4</td>
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<td>28.6</td>
<td>25</td>
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Table 2–32: Effectiveness TSQM derived score at end of treatment: full analysis set

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<tr>
<th></th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
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<tr>
<td><strong>Effectiveness score</strong></td>
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<td>Mean</td>
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<td>67.8</td>
<td>72.3</td>
<td>37.4</td>
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<td>SD</td>
<td>21.8</td>
<td>24.4</td>
<td>21.1</td>
<td>27.7</td>
</tr>
<tr>
<td>Median</td>
<td>66.7</td>
<td>72.2</td>
<td>77.8</td>
<td>33.3</td>
</tr>
<tr>
<td>Minimum</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum</td>
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<td>100</td>
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<td>Number</td>
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<td>48</td>
<td>56</td>
</tr>
<tr>
<td><strong>Comparisons versus vehicle</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference(^1)</td>
<td>30.97</td>
<td>30.38</td>
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</tr>
<tr>
<td>95% CI(^1)</td>
<td>21.67 to 40.26</td>
<td>21.20 to 39.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value(^1)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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1) Least Squares Means difference: From ANOVA with factors: treatment group and analysis site
### Table 2–33: Side Effects TSQM derived score at end of treatment: full analysis set

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<th>Side effect score</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>87.3</td>
<td>88.3</td>
<td>84.9</td>
<td>99.9</td>
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<tr>
<td><strong>SD</strong></td>
<td>18.8</td>
<td>23.2</td>
<td>22.8</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Minimum</strong></td>
<td>19</td>
<td>6</td>
<td>25</td>
<td>94</td>
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<tr>
<td><strong>Maximum</strong></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>55</td>
<td>58</td>
<td>48</td>
<td>58</td>
</tr>
</tbody>
</table>

**Comparisons versus vehicle**

| Difference¹ | -12.5 | -11.5 |
| 95% CI¹     | -18.92 to -18.92 | -17.81 to -17.81 |
| P-value²    | < 0.001 | < 0.001 |

¹ Least Squares Means difference: From ANOVA with factors: treatment group and analysis site.
### Table 2–34: Global Satisfaction TSQM derived score at end of treatment: full analysis set

<table>
<thead>
<tr>
<th></th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
<tbody>
<tr>
<td><strong>Global satisfaction score</strong></td>
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<tr>
<td>Mean</td>
<td>64.9</td>
<td>68.5</td>
<td>63.5</td>
<td>36.0</td>
</tr>
<tr>
<td>SD</td>
<td>23.7</td>
<td>25.2</td>
<td>24.8</td>
<td>27.7</td>
</tr>
<tr>
<td>Median</td>
<td>64.3</td>
<td>71.4</td>
<td>67.9</td>
<td>35.7</td>
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<td>Maximum</td>
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<td><strong>Comparisons versus vehicle</strong></td>
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<td></td>
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<tr>
<td>Difference¹</td>
<td>29.05</td>
<td>32.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI¹</td>
<td>19.52 to 38.58</td>
<td>23.24 to 42.06</td>
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<td>P-value¹</td>
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<td>&lt; 0.001</td>
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<td></td>
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¹ Least Squares Means difference: From ANOVA with factors: treatment group and analysis site
Table 2–35: Convenience TSQM derived score at end of treatment: full analysis set

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<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
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<tr>
<td>Mean</td>
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<td>79.1</td>
<td>77.7</td>
<td>78.7</td>
</tr>
<tr>
<td>SD</td>
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<td>17.0</td>
<td>14.1</td>
<td>15.3</td>
</tr>
<tr>
<td>Median</td>
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<td>Number</td>
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<tr>
<td>Comparisons versus vehicle</td>
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</tr>
<tr>
<td>Difference^1</td>
<td>1.28</td>
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<td></td>
</tr>
<tr>
<td>95% CI^1</td>
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<td>-5.14 to 6.28</td>
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<tr>
<td>P-value^1</td>
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</table>

1) Least Squares Means difference: From ANOVA with factors: treatment group and analysis site
Table 2–36: Complete clearance of AK 8 weeks after treatment (LOCF): full analysis set

<table>
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<tr>
<th>Complete clearance at 8 weeks</th>
<th>Ingenol 2 days (n=55)</th>
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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
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<td>5.1</td>
</tr>
<tr>
<td>No</td>
<td>48</td>
<td>87.3</td>
<td>56</td>
<td>94.9</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>100.0</td>
<td>59</td>
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</tbody>
</table>
### Table 2–37: Statistical analysis of complete clearance of AK 8 weeks after treatment (LOCF): full analysis set

<table>
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<tr>
<th>Treatment comparison</th>
<th>Relative risk[^1] [95% CI][^2]</th>
<th>P-value[^3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Global General association</td>
<td></td>
<td>P=0.021</td>
</tr>
<tr>
<td>b) Ingenol 3 days versus Vehicle[^2]</td>
<td>3.00 [0.61 to 14.86]</td>
<td>P=0.083</td>
</tr>
<tr>
<td>c) Ingenol 2 days versus Vehicle[^2]</td>
<td>3.54 [1.01 to 12.47]</td>
<td>P=0.004</td>
</tr>
<tr>
<td>d) Ingenol 3 days versus 2 days[^2]</td>
<td>0.47 [0.13 to 1.67]</td>
<td>P=0.22</td>
</tr>
</tbody>
</table>

[^1]: Adjusted for analysis site. Relative risk of complete clearance relative to vehicle group (b and c) and 2-day group (d).
[^2]: CMH logit estimators were used for comparisons with vehicle due to absence of cleared subject in the vehicle group.
[^3]: Type I error not controlled.
[^4]: Mantel-Haenszel estimators.
[^5]: P-value from Fishers Exact Test b)=0.12, c)=0.004, d)=0.19.
Table 2–38: Partial clearance of AK 8 weeks after treatment (LOCF): full analysis set

<table>
<thead>
<tr>
<th>Partial clearance at 8 weeks</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Yes</td>
<td>26</td>
<td>33</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>29</td>
<td>26</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>59</td>
<td>49</td>
<td>61</td>
</tr>
</tbody>
</table>
Table 2–39: Statistical analysis of partial clearance of AK 8 weeks after treatment (LOCF): full analysis set

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>Relative risk*</th>
<th>[95% CI]*</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Global General association</td>
<td>36.70</td>
<td>[4.92 to 273.9]</td>
<td>P=&lt; 0.001</td>
</tr>
<tr>
<td>b) Ingenol 3 days versus Vehicle</td>
<td>28.95</td>
<td>[3.84 to 218.4]</td>
<td>P=&lt; 0.001</td>
</tr>
<tr>
<td>c) Ingenol 2 days versus Vehicle</td>
<td>2.88</td>
<td>[0.86 to 1.65]</td>
<td>P=0.31</td>
</tr>
<tr>
<td>d) Ingenol 3 days versus 2 days</td>
<td>1.19</td>
<td>[0.86 to 1.65]</td>
<td>P=0.31</td>
</tr>
</tbody>
</table>

1) Adjusted for analysis site. Relative risk of partial clearance relative to vehicle group (b and c) and 2-day group (d)
2) Mantel-Haenszel estimators
Table 2–40: Reduction in AK count 8 weeks after treatment (LOCF): full analysis set

<table>
<thead>
<tr>
<th>AK count</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed mean</td>
<td>4.6</td>
<td>4.0</td>
<td>3.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Adjusted(^1) mean</td>
<td>4.1</td>
<td>3.6</td>
<td>3.6</td>
<td>9.8</td>
</tr>
<tr>
<td>Adjusted(^1) percentage</td>
<td>64.2</td>
<td>68.4</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>reduction from baseline</td>
<td>57.8</td>
<td>62.8</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Lower 95% CI</td>
<td>69.7</td>
<td>73.1</td>
<td>23.5</td>
<td></td>
</tr>
</tbody>
</table>

1) From negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset
Table 2–41: Statistical analysis of AK count 8 weeks after treatment (LOCF): full analysis set

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>Ratio of adjusted means</th>
<th>[95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ingenol 3 days versus Vehicle</td>
<td>0.37</td>
<td>[0.30 to 0.45]</td>
<td>P=&lt; 0.001</td>
</tr>
<tr>
<td>b) Ingenol 2 days versus Vehicle</td>
<td>0.41</td>
<td>[0.34 to 0.51]</td>
<td>P=&lt; 0.001</td>
</tr>
<tr>
<td>c) Ingenol 3 days versus Ingenol 2 days</td>
<td>0.88</td>
<td>[0.70 to 1.11]</td>
<td>P=0.29</td>
</tr>
</tbody>
</table>

1) From negative binomial regression model with factors treatment and analysis site and with log of baseline AK count as offset.
Table 2–42: Complete clearance of AK 8 weeks after treatment on arms and back of hands (observed case): full analysis set

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Arm excluding back of hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>12</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>22.0</td>
<td>24.0</td>
<td>33.3</td>
<td>0.0</td>
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<tr>
<td>No</td>
<td>39</td>
<td>38</td>
<td>28</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>78.0</td>
<td>76.0</td>
<td>66.7</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
<td>42</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Back of hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>21.9</td>
<td>23.3</td>
<td>35.7</td>
<td>4.2</td>
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<tr>
<td>No</td>
<td>25</td>
<td>23</td>
<td>18</td>
<td>23</td>
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<tr>
<td></td>
<td>78.1</td>
<td>76.7</td>
<td>64.3</td>
<td>95.8</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>30</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

1) The arm excluding back of hand location includes subjects treated on arm excluding back of hand and subjects treated on arm including back of hand
2) The same subject may appear in both categories
Table 2–43: Partial clearance of AK 8 weeks after treatment on arms and back of hands (observed case): full analysis set

<table>
<thead>
<tr>
<th>Location</th>
<th>Location</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm</td>
<td></td>
<td>Roy</td>
<td>Roy</td>
<td>Roy</td>
<td>Roy</td>
</tr>
<tr>
<td></td>
<td>excluding back of hand</td>
<td>Yes</td>
<td>60.0</td>
<td>66.0</td>
<td>64.3</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>40.0</td>
<td>34.0</td>
<td>35.7</td>
<td>98.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>Yes</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
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<tr>
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<td>46.7</td>
<td>53.6</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>59.4</td>
<td>53.3</td>
<td>46.4</td>
<td>95.8</td>
</tr>
<tr>
<td>Total</td>
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<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

1) The arm excluding back of hand location includes subjects treated on arm excluding back of hand and subjects treated on arm including back of hand
2) The same subject may appear in both categories
Table 2–44: Reduction in AK count 8 weeks after treatment on arms and back of hands (observed case): full analysis set

<table>
<thead>
<tr>
<th>Location</th>
<th>%Change in AK count</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm excluding back of hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<td>-71.0</td>
<td>-74.7</td>
<td>-10.8</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>37.1</td>
<td>34.4</td>
<td>32.2</td>
<td>42.0</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>-78.6</td>
<td>-80.0</td>
<td>-80.0</td>
<td>-7.7</td>
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</tr>
<tr>
<td>Minimum</td>
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<td>-100.0</td>
<td>-100.0</td>
<td>-77.8</td>
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</tr>
<tr>
<td>Maximum</td>
<td>40.0</td>
<td>80.0</td>
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<td>200.0</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>49</td>
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<td>42</td>
<td>49</td>
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<tr>
<td>Back of hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-55.9</td>
<td>-68.6</td>
<td>-63.8</td>
<td>-7.4</td>
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</tr>
<tr>
<td>SD</td>
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<td>40.9</td>
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<td>-100.0</td>
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<tr>
<td>Maximum</td>
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<td>80.0</td>
<td>80.0</td>
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<tr>
<td>Number</td>
<td>32</td>
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<td>27</td>
<td>24</td>
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</tr>
</tbody>
</table>

1) The arm excluding back of hand location includes subjects treated on arm excluding back of hand and subjects treated on arm including back of hand
2) The same subject may appear in both categories
Table 2–45: Baseline and change from baseline in individual photo-damage characteristics: full analysis set

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Visit</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
<tbody>
<tr>
<td>Coarse Wrinkling</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>Mean</td>
<td>1.4</td>
<td>1.1</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>SD</td>
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<td>0.8</td>
<td>1.0</td>
<td>0.8</td>
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<tr>
<td></td>
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<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
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<td>Number</td>
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<td>61</td>
</tr>
<tr>
<td>Day 56</td>
<td>Mean</td>
<td>1.1</td>
<td>1.0</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.8</td>
<td>0.7</td>
<td>0.8</td>
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</tr>
<tr>
<td></td>
<td>Median</td>
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</tr>
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<td>Number</td>
<td>55</td>
<td>58</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td>Day 56 change from baseline</td>
<td>Mean</td>
<td>-0.3</td>
<td>-0.2</td>
<td>-0.3</td>
<td>0.2</td>
</tr>
<tr>
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<td>SD</td>
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<tr>
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<td>Minimum</td>
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<td>-2</td>
<td>-2</td>
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<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>55</td>
<td>58</td>
<td>48</td>
<td>58</td>
</tr>
</tbody>
</table>

Continued...
Table 2-45: Baseline and change from baseline in individual photo-damage characteristics: full analysis set (continued)

<table>
<thead>
<tr>
<th>Photo Damage Parameter</th>
<th>Visit</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine Wrinkling</td>
<td>Day 1</td>
<td>Mean: 1.2</td>
<td>Mean: 1.3</td>
<td>Mean: 1.5</td>
<td>Mean: 1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD: 0.7</td>
<td>SD: 0.7</td>
<td>SD: 0.8</td>
<td>SD: 0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median: 1.0</td>
<td>Median: 1.0</td>
<td>Median: 1.0</td>
<td>Median: 1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimum: 0</td>
<td>Minimum: 0</td>
<td>Minimum: 0</td>
<td>Minimum: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum: 3</td>
<td>Maximum: 4</td>
<td>Maximum: 3</td>
<td>Maximum: 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number: 55</td>
<td>Number: 59</td>
<td>Number: 49</td>
<td>Number: 61</td>
</tr>
<tr>
<td>Day 56</td>
<td>Mean: 1.1</td>
<td>Mean: 1.0</td>
<td>Mean: 1.2</td>
<td>Mean: 1.4</td>
<td>Mean: 1.4</td>
</tr>
<tr>
<td></td>
<td>SD: 0.7</td>
<td>SD: 0.6</td>
<td>SD: 0.7</td>
<td>SD: 0.7</td>
<td>SD: 0.6</td>
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<tr>
<td></td>
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<td>Median: 1.0</td>
<td>Median: 1.0</td>
<td>Median: 1.0</td>
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<td></td>
<td>Maximum: 3</td>
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<td></td>
<td>Number: 55</td>
<td>Number: 58</td>
<td>Number: 48</td>
<td>Number: 58</td>
<td>Number: 58</td>
</tr>
<tr>
<td>Day 56 change from baseline</td>
<td>Mean: -0.1</td>
<td>Mean: -0.3</td>
<td>Mean: -0.4</td>
<td>Mean: 0.1</td>
<td>Mean: 0.1</td>
</tr>
<tr>
<td></td>
<td>SD: 0.7</td>
<td>SD: 0.6</td>
<td>SD: 0.6</td>
<td>SD: 0.7</td>
<td>SD: 0.7</td>
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<tr>
<td></td>
<td>Median: 0.0</td>
<td>Median: 0.0</td>
<td>Median: 0.0</td>
<td>Median: 0.0</td>
<td>Median: 0.0</td>
</tr>
<tr>
<td></td>
<td>Maximum: 2</td>
<td>Maximum: 1</td>
<td>Maximum: 1</td>
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<td>Number: 55</td>
<td>Number: 58</td>
<td>Number: 48</td>
<td>Number: 58</td>
<td>Number: 58</td>
</tr>
</tbody>
</table>
Table 2-45: Baseline and change from baseline in individual photo-damage characteristics: full analysis set (continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Visit</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mottled Pigmentation</td>
<td>Day 1</td>
<td>Mean: 1.8, SD: 0.8, Median: 2.0, Minimum: 0, Maximum: 4, Number: 55</td>
<td>Mean: 1.7, SD: 0.8, Median: 2.0, Minimum: 0, Maximum: 3, Number: 59</td>
<td>Mean: 1.8, SD: 0.6, Median: 2.0, Minimum: 1, Maximum: 3, Number: 49</td>
<td>Mean: 1.7, SD: 0.7, Median: 2.0, Minimum: 0, Maximum: 3, Number: 61</td>
</tr>
<tr>
<td></td>
<td>Day 56</td>
<td>Mean: 1.5, SD: 0.9, Median: 1.0, Minimum: 0, Maximum: 4, Number: 55</td>
<td>Mean: 1.3, SD: 0.6, Median: 1.0, Minimum: 0, Maximum: 3, Number: 58</td>
<td>Mean: 1.2, SD: 0.7, Median: 1.0, Minimum: 3, Maximum: 3, Number: 48</td>
<td>Mean: 1.6, SD: 0.8, Median: 2.0, Minimum: 3, Maximum: 3, Number: 58</td>
</tr>
<tr>
<td>Day 56 change from baseline</td>
<td>Mean: -0.3, SD: 0.8, Median: 0.0, Minimum: -2, Maximum: 2, Number: 55</td>
<td>Mean: -0.3, SD: 0.7, Median: -1.0, Minimum: -2, Maximum: 1, Number: 58</td>
<td>Mean: -0.6, SD: 0.7, Median: -2, Minimum: -2, Maximum: 1, Number: 48</td>
<td>Mean: 0.0, SD: 0.5, Median: 0.0, Minimum: -2, Maximum: -2, Number: 58</td>
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</tr>
</tbody>
</table>
### Table 2-45: Baseline and change from baseline in individual photo-damage characteristics: full analysis set (continued)

<table>
<thead>
<tr>
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Table 2-45: Baseline and change from baseline in individual photo-damage characteristics: full analysis set (continued)

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Table 2-45: Baseline and change from baseline in individual photo-damage characteristics: full analysis set (continued)

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Table 2–46: Photo-damage characteristics by individual categories and visit: full analysis set

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Table 2-46: Photo-damage characteristics by individual categories and visit: full analysis set (continued)

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Table 2-46: Photo-damage characteristics by individual categories and visit: full analysis set (continued)

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Table 2-46: Photo-damage characteristics by individual categories and visit: full analysis set (continued)

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Table 2-46: Photo-damage characteristics by individual categories and visit: full analysis set (continued)

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Table 2-46: Photo-damage characteristics by individual categories and visit: full analysis set (continued)

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<td>Ingenol 4 days (n=49)</td>
<td>Vehicle (n=61)</td>
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Table 2-49: Subject’s cosmetic outcome categories: full analysis set

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<th>Cosmetic outcome</th>
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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>Number of subjects</td>
<td>%</td>
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<tr>
<td>Worsened</td>
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<td>No change</td>
<td>6</td>
<td>10.9</td>
<td>11</td>
<td>19.0</td>
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<td>Somewhat improved</td>
<td>28</td>
<td>50.9</td>
<td>26</td>
<td>44.8</td>
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<tr>
<td>Much improved</td>
<td>20</td>
<td>36.4</td>
<td>21</td>
<td>36.2</td>
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<tr>
<td>Total</td>
<td>55</td>
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<td>58</td>
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<td></td>
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<tr>
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<td>36.4</td>
<td>20</td>
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<tr>
<td>Much improved</td>
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Table 2–50: Absolute reduction in AK count by visit (observed case): full analysis set

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<tr>
<th>Visit Change in AK count</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
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<th>Vehicle (n=61)</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
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<td>Day 31</td>
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<td>-7.0</td>
<td>-9.0</td>
<td>-1.0</td>
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<tr>
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<td>-20</td>
<td>-19</td>
<td>-13</td>
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<td>58</td>
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### Table 2–51: Reduction in AK count 8 weeks after treatment by baseline count class (observed case): full analysis set

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<tr>
<th>Baseline count class</th>
<th>%Change in AK count</th>
<th>Ingenol 2 days (n=55)</th>
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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<tbody>
<tr>
<td>5-9</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>16</td>
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<tr>
<td>10-20</td>
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<td></td>
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### Table 2–52: Complete clearance of AK 8 weeks after treatment by baseline AK count class (observed case): full analysis set

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<th>Baseline count class</th>
<th>Complete clearance</th>
<th>Ingenol 2 days (n=55)</th>
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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
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Figure 2-1: Complete clearance of AKs by treatment group and visit (observed cases)
Figure 2-2: Reduction in AK count by treatment group and visit (observed cases)
Figure 2-3: Partial clearance of AKs by treatment group and visit (observed cases)

Day 31/Week 4
- Vehicle: 3.6%
- Ingenol 2 days: 40.7%
- Ingenol 3 days: 41.4%
- Ingenol 4 days: 60.4%

Day 56/Week 8
- Vehicle: 1.7%
- Ingenol 2 days: 47.3%
- Ingenol 3 days: 56.9%
- Ingenol 4 days: 60.4%
Figure 2-4: Complete clearance of AKs by treatment group at week 8 (observed cases)
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Table 3–1: Overall summary of adverse events: safety analysis set

<table>
<thead>
<tr>
<th>Adverse event category</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of AEs¹</td>
<td>Number of subjects (%)</td>
<td>Number of AEs¹</td>
<td>Number of subjects (%)</td>
</tr>
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<td>All adverse events</td>
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<td>49 (89.1)</td>
<td>126</td>
<td>57 (96.6)</td>
</tr>
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<td>6 (10.2)</td>
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<td>49 (89.1)</td>
<td>106</td>
<td>57 (96.6)</td>
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<td>55 (93.2)</td>
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<td>5</td>
<td>5 ( 8.5)</td>
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¹ Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one.
### Table 3–2: Adverse events by SOC: safety analysis set

<table>
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<tr>
<th>System Organ Class</th>
<th>Ingenol 2 days (n=55)</th>
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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<tr>
<td>General disorders and administration site conditions</td>
<td>48 87.3</td>
<td>54 91.5</td>
<td>47 95.9</td>
<td>6 9.8</td>
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<tr>
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<td>7 11.9</td>
<td>13 26.5</td>
<td>5 8.2</td>
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<td>8 16.3</td>
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<td>5 8.2</td>
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<td>2 3.4</td>
<td>2 4.1</td>
<td>4 6.6</td>
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<td>Injury, poisoning and procedural complications</td>
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<td>2 3.3</td>
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<td>0 0.0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
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<td>1 2.0</td>
<td>1 1.6</td>
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<tr>
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<td>2 4.1</td>
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</tr>
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<td>Respiratory, thoracic and mediastinal disorders</td>
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<td>1 1.7</td>
<td>1 2.0</td>
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<td>0 0.0</td>
<td>0 0.0</td>
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<td>Reproductive system and breast disorders</td>
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<tr>
<td><strong>Total number of adverse events</strong></td>
<td><strong>99</strong></td>
<td><strong>126</strong></td>
<td><strong>121</strong></td>
<td><strong>39</strong></td>
</tr>
<tr>
<td><strong>Total number of subjects</strong></td>
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<td><strong>57</strong></td>
<td><strong>96.6</strong></td>
<td><strong>28</strong></td>
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</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
3) n=Number of subjects
Table 3–3: Adverse events by SOC and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
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<td></td>
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<td>3</td>
<td>5.1</td>
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<tr>
<td>Application site warmth</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
<td>1.7</td>
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<td>0.0</td>
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<td>Pain</td>
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<td>0.0</td>
<td>1</td>
<td>1.7</td>
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<td>Application site haematoma</td>
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<td>1.7</td>
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<tr>
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<td></td>
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<tr>
<td>Squamous cell carcinoma of skin</td>
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<tr>
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Table 3-3: Adverse events by SOC and preferred term: safety analysis set (continued)

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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
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<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
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<td>0.0</td>
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</tr>
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<td></td>
<td></td>
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Continued...
Table 3-3: Adverse events by SOC and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<tbody>
<tr>
<td></td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
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<tr>
<td><strong>Infections and infestations</strong></td>
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<td>Tinea cruris</td>
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<td>7 14.3</td>
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<tr>
<td>System Organ Class (SOC)</td>
<td>Ingenol 2 days (n=55)</td>
<td>Ingenol 3 days (n=59)</td>
<td>Ingenol 4 days (n=49)</td>
<td>Vehicle (n=61)</td>
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<td>%</td>
<td>Number of subjects</td>
<td>%</td>
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<td>Skin and subcutaneous tissue disorders</td>
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19DEC14:11:52:27 LP0105-1020 t03_aept.doc Continued...
Table 3-3: Adverse events by SOC and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>Number of subjects</td>
<td>Number of subjects</td>
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<tr>
<td></td>
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<td>%</td>
<td>%</td>
<td>%</td>
</tr>
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<td>Nervous system disorders</td>
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<td>4.1</td>
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Table 3-3: Adverse events by SOC and preferred term: safety analysis set (continued)

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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>%</td>
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Table 3-3: Adverse events by SOC and preferred term: safety analysis set (continued)

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<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td></td>
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<td>%</td>
<td>Number of subjects</td>
<td>%</td>
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<td>Lacrimation increased</td>
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Table 3-3: Adverse events by SOC and preferred term: safety analysis set (continued)

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<th>System Organ Class (SOC)</th>
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<th>%</th>
<th>Number of subjects</th>
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1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Table 3–4: Adverse events observed in >= 5% of subjects by SOC and preferred term:
safety analysis set

<table>
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<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
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<th>Vehicle (n=61)</th>
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<tr>
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<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
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1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Table 3–5: Adverse drug reactions by SOC and preferred term: safety analysis set

<table>
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<td>Number of subjects %</td>
<td>Number of subjects %</td>
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Skin and subcutaneous tissue disorders:

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### Table 3-5: Adverse drug reactions by SOC and preferred term: safety analysis set (continued)

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### Table 3-5: Adverse drug reactions by SOC and preferred term: safety analysis set (continued)

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<td>Application site oedema</td>
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<td>1 2.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td></td>
<td>SOC total</td>
<td>1 1.8 1 1.7</td>
<td>1 2.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>0 0.0 1 1.7</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td></td>
<td>Nightmare</td>
<td>0 0.0 1 1.7</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
<td>0 0.0 0 0.0</td>
<td>0 0.0</td>
<td>1 2.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td></td>
<td>Sleep disorder</td>
<td>0 0.0 0 0.0</td>
<td>1 2.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td></td>
<td>SOC total</td>
<td>0 0.0 2 3.4</td>
<td>1 2.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Blepharitis</td>
<td>0 0.0 0 0.0</td>
<td>1 2.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td></td>
<td>Eye pain</td>
<td>1 1.8 0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td></td>
<td>Lacrimation</td>
<td>0 0.0 0 0.0</td>
<td>0 0.0</td>
<td>1 2.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td></td>
<td>SOC total</td>
<td>1 1.8 0 0.0</td>
<td>1 2.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperkalaemia</td>
<td>1 1.8 0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
</tbody>
</table>

Continued...
Table 3-5: Adverse drug reactions by SOC and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred Term(^1)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOC total</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Total number of drug reactions(^2)</td>
<td>88</td>
<td>106</td>
<td>91</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>49</td>
<td>89.1</td>
<td>57</td>
<td>96.6</td>
<td>48</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse drug reactions within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Table 3–6: Adverse drug reactions observed in >= 5% of subjects by SOC and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class (SOC) Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site pain</td>
<td>45</td>
<td>81.8</td>
<td>50</td>
<td>84.7</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>19</td>
<td>34.5</td>
<td>27</td>
<td>45.8</td>
</tr>
<tr>
<td>Application site discomfort</td>
<td>2</td>
<td>3.6</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>SOC total</td>
<td>48</td>
<td>87.3</td>
<td>54</td>
<td>91.5</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma of skin</td>
<td>2</td>
<td>3.6</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>SOC total</td>
<td>2</td>
<td>3.6</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>SOC total</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>Total number of adverse events</td>
<td>68</td>
<td>87.3</td>
<td>86</td>
<td>93.2</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>48</td>
<td>87.3</td>
<td>55</td>
<td>93.2</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse drug reactions within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Table 3–7: Serious adverse events by SOC and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma of skin</td>
<td>3 5.5</td>
<td>4 6.8</td>
<td>3 6.1</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>1 2.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>SOC total</td>
<td>3 5.5</td>
<td>4 6.8</td>
<td>4 8.2</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>0 0.0</td>
<td>1 1.7</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>SOC total</td>
<td>0 0.0</td>
<td>1 1.7</td>
<td>0 0.0</td>
<td>0 0.0</td>
</tr>
<tr>
<td>Total number of Serious adverse events²</td>
<td>3 5.5</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>3 5.5</td>
<td>5 8.5</td>
<td>4 8.2</td>
<td>0 0.0</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Table 3–8: Adverse events leading to withdrawal from trial by SOC and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>SOC total</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Total number of adverse events^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Table 3–9: Adverse events leading to discontinuation of treatment by SOC and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Application site pain</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Application site hypersensitivity</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>SOC total</td>
<td>1</td>
<td>1.8</td>
<td>4</td>
<td>6.8</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Application site infection</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>SOC total</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Eczema</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>SOC total</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total number of adverse events</td>
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<td>2</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td></td>
<td>1</td>
<td>1.8</td>
<td>4</td>
<td>6.8</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Table 3–10: Non-serious adverse events by medDRA Primary System Organ Class (SOC) and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred Term</th>
<th>Number of subjects (n=55)</th>
<th>Percentage</th>
<th>Number of subjects (n=59)</th>
<th>Percentage</th>
<th>Number of subjects (n=49)</th>
<th>Percentage</th>
<th>Number of subjects (n=61)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Application site pain</td>
<td>45</td>
<td>81.8</td>
<td>50</td>
<td>84.7</td>
<td>43</td>
<td>87.8</td>
<td>3</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>Application site pruritus</td>
<td>19</td>
<td>34.5</td>
<td>27</td>
<td>45.8</td>
<td>14</td>
<td>28.6</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Application site discomfort</td>
<td>2</td>
<td>3.6</td>
<td>3</td>
<td>5.1</td>
<td>2</td>
<td>4.1</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Application site warmth</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
<td>1.7</td>
<td>1</td>
<td>2.0</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Application site discomfort</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>4.1</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Pain</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
<td>1</td>
<td>2.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Application site haematoma</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Application site hypersensitivity</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Application site irritation</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Application site paraesthesia</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>2.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Swelling</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>SOC total</td>
<td>48</td>
<td>87.3</td>
<td>54</td>
<td>91.5</td>
<td>47</td>
<td>95.9</td>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>1</td>
<td>1.8</td>
<td>2</td>
<td>3.4</td>
<td>2</td>
<td>4.1</td>
<td>3</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>Application site infection</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>3.4</td>
<td>1</td>
<td>2.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
<td>1</td>
<td>2.0</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Table 3-10: Non-serious adverse events by medDRA Primary System Organ Class (SOC) and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folliculitis</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Impetigo</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Rash pustular</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Staphylococcal skin</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinea cruris</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Wound infection</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>SOC total</td>
<td>36</td>
<td>5.5</td>
<td>6</td>
<td>10.2</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>2</td>
<td>3.6</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Eczema</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Rash pruritic</td>
<td>1</td>
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Table 3-10: Non-serious adverse events by medDRA Primary System Organ Class (SOC) and preferred term: safety analysis set (continued)

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Table 3-10: Non-serious adverse events by medDRA Primary System Organ Class (SOC) and preferred term: safety analysis set (continued)

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Table 3-10: Non-serious adverse events by medDRA Primary System Organ Class (SOC) and preferred term: safety analysis set (continued)

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Table 3-10: Non-serious adverse events by medDRA Primary System Organ Class (SOC) and preferred term: safety analysis set (continued)

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Table 3-10: Non-serious adverse events by medDRA Primary System Organ Class (SOC) and preferred term: safety analysis set (continued)

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1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Table 3–11: Application site pain by LLT: safety analysis set

<table>
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<tr>
<th>Lowest Level Term(^1)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<tr>
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1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same lowest level term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
3) n=Number of subjects
Table 3–12: Intensity of adverse events by SOC and preferred term: safety analysis set

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<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td></td>
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<td>Mod</td>
<td>Sev</td>
<td>Mild</td>
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<td>General disorders and administration site conditions</td>
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19DEC14:11:53:25 LP0105 1020 t12_aept_sev.doc
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Table 3-12: Intensity of adverse events by SOC and preferred term: safety analysis set (continued)

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Table 3-12: Intensity of adverse events by SOC and preferred term: safety analysis set (continued)

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<th>System Organ Class (SOC)</th>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
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<th>Ingenol 4 days (n=49)</th>
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<td>Sev¹</td>
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Table 3-12: Intensity of adverse events by SOC and preferred term: safety analysis set (continued)

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<th>System Organ Class (SOC)</th>
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<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td></td>
<td>Mild</td>
<td>Mod</td>
<td>Sev</td>
<td>Mild</td>
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Table 3-12: Intensity of adverse events by SOC and preferred term: safety analysis set (continued)

<table>
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<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Mild</td>
<td>Mod</td>
<td>Sev</td>
<td>Mild</td>
</tr>
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</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
3) Mod=Moderate, Sev=Severe
Table 3–13: Intensity of application site pain by LLT: safety analysis set

<table>
<thead>
<tr>
<th>Lowest Level Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mil</td>
<td>Mod</td>
<td>Sev</td>
<td>Mil</td>
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<tr>
<td>Application site burning</td>
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<td>11</td>
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<td>Application site pain</td>
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<td>Application site stinging</td>
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<td>Total number of adverse events</td>
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<td>13</td>
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1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same lowest level term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
3) Mod=Moderate, Sev=Severe
### Table 3–14: Relationship to investigational product by SOC and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
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<td>Application site inflammation</td>
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<td>Pain</td>
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<td>Application site haematoma</td>
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<td>Application site hypersensitivity</td>
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<td>Malaise</td>
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Continued...
### Table 3-14: Relationship to investigational product by SOC and preferred term: safety analysis set (continued)

<table>
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<tr>
<th>System Organ Class (SOC)</th>
<th>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</th>
<th>Skin and subcutaneous tissue disorders</th>
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</thead>
<tbody>
<tr>
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<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Skin and subcutaneous tissue disorders</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma of skin</td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td>Basal cell carcinoma</td>
<td>Eczema</td>
</tr>
<tr>
<td></td>
<td>Bowen's disease</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>Seborrhoeic keratosis</td>
<td>Rash pruritic</td>
</tr>
<tr>
<td></td>
<td>Keratoacanthoma</td>
<td>Actinic keratosis</td>
</tr>
<tr>
<td></td>
<td>Dysplastic naevus</td>
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<tr>
<td></td>
<td>Malignant melanoma</td>
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</tr>
<tr>
<td></td>
<td>Acanthoma</td>
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<td>Basosquamous carcinoma of skin</td>
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**Ingenol 2 days (n=55)**

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### Table 3-14: Relationship to investigational product by SOC and preferred term: safety analysis set (continued)

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<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred Term</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
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Table 3-14: Relationship to investigational product by SOC and preferred term: safety analysis set (continued)

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<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
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Table 3-14: Relationship to investigational product by SOC and preferred term: safety analysis set (continued)

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<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
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<td>Paraesthesia oral</td>
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Continued...
Table 3-14: Relationship to investigational product by SOC and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
<tbody>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
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<tr>
<td>Accidental exposure</td>
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<td>Laceration</td>
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<td>Application site oedema</td>
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<td>Wound</td>
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<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
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<td>Pain in extremity</td>
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<td><strong>Eye disorders</strong></td>
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<td>Blepharitis</td>
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<td>Lacrimation increased</td>
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<td><strong>Metabolism and nutrition disorders</strong></td>
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19DEC14:11:53:45 LP0105 1020 t14_aerel.doc Continued...
Table 3-14: Relationship to investigational product by SOC and preferred term: safety analysis set (continued)

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<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
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<td>Gout</td>
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<td>Psychiatric disorders</td>
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<td>Insomnia</td>
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<td>Nightmare</td>
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<td>Restlessness</td>
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<td>Sleep disorder</td>
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<td>0</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
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<td>Atelectasis</td>
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<td>0</td>
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<td>Rhinitis allergic</td>
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<td>0</td>
<td>0</td>
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<td>Sinus congestion</td>
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<td>Cardiac disorders</td>
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<td>Coronary artery disease</td>
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<td>Reproductive system and breast disorders</td>
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<td>Prostatitis</td>
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Table 3-14: Relationship to investigational product by SOC and preferred term: safety analysis set (continued)

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
<tbody>
<tr>
<td>Total number of adverse events</td>
<td>11</td>
<td>0</td>
<td>28</td>
<td>60</td>
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</tbody>
</table>

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
3) Not rel.: Not related; Not Ass.: Not assessable; Poss.: Possible; Prob.: Probable.
Table 3–15: LSRs that worsen in intensity after baseline converted to medDRA Primary System Organ Class (SOC) and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
</tr>
<tr>
<td>GENERAL DISORDERS AND ADMINISTRATION SITE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site erythema</td>
<td>53 96.4</td>
<td>55 93.2</td>
<td>47 95.9</td>
<td>11 18.0</td>
</tr>
<tr>
<td>Application site exfoliation</td>
<td>49 89.1</td>
<td>50 84.7</td>
<td>48 98.0</td>
<td>10 16.4</td>
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<tr>
<td>Application site scab</td>
<td>49 89.1</td>
<td>47 79.7</td>
<td>44 89.8</td>
<td>13 21.3</td>
</tr>
<tr>
<td>Application site swelling</td>
<td>46 83.6</td>
<td>46 78.0</td>
<td>45 91.8</td>
<td>2 3.3</td>
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<tr>
<td>Application site swelling</td>
<td>28 50.9</td>
<td>35 59.3</td>
<td>36 73.5</td>
<td>1 1.6</td>
</tr>
<tr>
<td>Application site pustules</td>
<td>24 43.6</td>
<td>31 52.5</td>
<td>33 67.3</td>
<td>2 3.3</td>
</tr>
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<td>Application site vesicles</td>
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<td>0 0.0</td>
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</tr>
<tr>
<td>SOC total</td>
<td>54 98.2</td>
<td>57 96.6</td>
<td>48 98.0</td>
<td>24 39.3</td>
</tr>
</tbody>
</table>

Total number of adverse events 268 285 269 39
Total number of subjects 54 98.2 57 96.6 48 98.0 24 39.3

1) Classification according to MedDRA version 15.1.
2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
### Table 3–16: Local skin response by individual categories and visit: safety analysis set

<table>
<thead>
<tr>
<th>Skin response parameter</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td></td>
<td>n¹</td>
<td>%</td>
<td>n¹</td>
<td>%</td>
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<tr>
<td><strong>Erythema</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>22</td>
<td>40.0</td>
<td>23</td>
<td>39.0</td>
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<tr>
<td>Slightly pink &lt;50%</td>
<td>31</td>
<td>56.4</td>
<td>32</td>
<td>54.2</td>
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<tr>
<td>Pink or light red &gt;50%</td>
<td>2</td>
<td>3.6</td>
<td>4</td>
<td>6.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>55</td>
<td>100.0</td>
<td>59</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Day 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Not present</td>
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<td>0</td>
<td>0.0</td>
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<tr>
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<td>7.3</td>
<td>7</td>
<td>11.9</td>
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<tr>
<td>Pink or light red &gt;50%</td>
<td>21</td>
<td>38.2</td>
<td>18</td>
<td>30.5</td>
</tr>
<tr>
<td>Red, restricted to treatment area</td>
<td>25</td>
<td>45.5</td>
<td>28</td>
<td>47.5</td>
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<tr>
<td>Red extending outside treatment area</td>
<td>5</td>
<td>9.1</td>
<td>6</td>
<td>10.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>55</td>
<td>100.0</td>
<td>59</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Day 10</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>3</td>
<td>5.5</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Slightly pink &lt;50%</td>
<td>12</td>
<td>21.8</td>
<td>14</td>
<td>23.7</td>
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<tr>
<td>Pink or light red &gt;50%</td>
<td>19</td>
<td>34.5</td>
<td>17</td>
<td>28.8</td>
</tr>
<tr>
<td>Red, restricted to treatment area</td>
<td>19</td>
<td>34.5</td>
<td>21</td>
<td>35.6</td>
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<tr>
<td>Red extending outside treatment area</td>
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<td>3.6</td>
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<td><strong>Total</strong></td>
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<td>59</td>
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Table 3-16: Local skin response by individual categories and visit: safety analysis set (continued)

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<th>Ingenol 2 days (n=55)</th>
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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td>%</td>
<td>n¹</td>
<td>%</td>
</tr>
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<td>Erythema</td>
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<td></td>
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<tr>
<td>Day 17</td>
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<td>10.9</td>
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<td>8.5</td>
</tr>
<tr>
<td>Slightly pink &lt;50%</td>
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<td>27</td>
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<td>32.2</td>
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<td>Pink or light red &gt;50%</td>
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<td>21.8</td>
<td>25</td>
<td>42.4</td>
</tr>
<tr>
<td>Red, restricted to treatment area</td>
<td></td>
<td>10</td>
<td>18.2</td>
<td>9</td>
<td>15.3</td>
</tr>
<tr>
<td>Red extending outside treatment area</td>
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<td>0.0</td>
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<td>1.7</td>
</tr>
<tr>
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<td></td>
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<td>59</td>
<td>100.0</td>
</tr>
<tr>
<td>Day 31</td>
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<td>13</td>
<td>24.1</td>
<td>13</td>
<td>22.4</td>
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<td>38.2</td>
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<td>56.4</td>
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<td>Pink or light red &gt;50%</td>
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<td>5.5</td>
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<td>Flaking/Scaling</td>
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</tr>
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<td>Day 1</td>
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<td></td>
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<tr>
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<td></td>
<td>17</td>
<td>30.9</td>
<td>14</td>
<td>23.7</td>
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</table>
Table 3-16: Local skin response by individual categories and visit: safety analysis set (continued)

<table>
<thead>
<tr>
<th>Skin response parameter</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<tbody>
<tr>
<td></td>
<td>n^1</td>
<td>%</td>
<td>n^1</td>
<td>%</td>
</tr>
<tr>
<td>Flaking/Scaling</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Isolated scale, specific to lesions</td>
<td>37</td>
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<td>42</td>
<td>71.2</td>
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<td>Scale &lt;50%</td>
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<td>1.8</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>Total</td>
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<td>100.0</td>
<td>59</td>
<td>100.0</td>
</tr>
<tr>
<td>Day 5</td>
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<tr>
<td>Isolated scale, specific to lesions</td>
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<td>9.1</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>Scale &lt;50%</td>
<td>31</td>
<td>56.4</td>
<td>25</td>
<td>42.4</td>
</tr>
<tr>
<td>Scale &gt;50%</td>
<td>16</td>
<td>29.1</td>
<td>23</td>
<td>39.0</td>
</tr>
<tr>
<td>Total</td>
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<td>100.0</td>
<td>59</td>
<td>100.0</td>
</tr>
<tr>
<td>Day 10</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated scale, specific to lesions</td>
<td>19</td>
<td>34.5</td>
<td>16</td>
<td>27.1</td>
</tr>
<tr>
<td>Scale &lt;50%</td>
<td>17</td>
<td>30.9</td>
<td>22</td>
<td>37.3</td>
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Table 3-16: Local skin response by individual categories and visit: safety analysis set (continued)

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Table 3-16: Local skin response by individual categories and visit: safety analysis set (continued)

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Table 3-16: Local skin response by individual categories and visit: safety analysis set (continued)

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Table 3-16: Local skin response by individual categories and visit: safety analysis set (continued)

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Table 3-16: Local skin response by individual categories and visit: safety analysis set (continued)

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<th>Vehicle (n=61)</th>
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<td>3 6.3</td>
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Table 3-16: Local skin response by individual categories and visit: safety analysis set (continued)

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1) n=Number of subjects
Table 3–17: Maximal local skin response score (LSR) post baseline by individual categories: safety analysis set

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Table 3-17: Maximal local skin response score (LSR) post baseline by individual categories: safety analysis set (continued)

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<th>Category</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
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Table 3–18: Maximal local skin response score (LSR) post baseline by individual categories and by country: safety analysis set

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<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
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Table 3-18: Maximal local skin response score (LSR) post baseline by individual categories and by country: safety analysis set (continued)

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Table 3-18: Maximal local skin response score (LSR) post baseline by individual categories and by country: safety analysis set (continued)

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Table 3-18: Maximal local skin response score (LSR) post baseline by individual categories and by country: safety analysis set (continued)

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Table 3–19: Maximal local skin response post baseline by individual categories: safety analysis set

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Table 3-19: Maximal local skin response post baseline by individual categories: safety analysis set (continued)

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<tr>
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1) n=Number of subjects
### Table 3–20: Summary of composite score (LSR) by visit: safety analysis set

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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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Table 3-20: Summary of composite score (LSR) by visit: safety analysis set (continued)

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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>SD</td>
<td>Mean</td>
<td>SD</td>
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<td>Maximum</td>
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<td>58</td>
<td>48</td>
<td>57</td>
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</table>

|       |                     | Mean                   | SD                    | Mean                 | SD            |
| Day 56|                     | 1.5                    | 1.2                   | 1.4                  | 1.0           |
|       | Median              | 1.0                    | 1.0                   | 2.0                  | 1.1           |
|       | Minimum             | 5                      | 0                     | 0                    | 0             |
|       | Maximum             | 55                     | 58                    | 48                   | 58            |

| Maximum post-baseline LSR score | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  | Mean | SD  |
|---------------------------------|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|
|                                 | 8.8  | 3.3 | 9.5  | 4.2 | 12.4 | 4.3 | 2.2  | 1.7 | 2.0  | 1.7 | 22   | 9   | 48   | 59  | 48   | 59  | 48   | 59  | 48   | 59  | 48   | 59  | 48   | 59  | 48   | 59  | 48   | 59  |
### Table 3–21: Summary of composite score (LSR) change from baseline by visit: safety analysis set

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Table 3-21: Summary of composite score (LSR) change from baseline by visit: safety analysis set (continued)

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## Table 3–22: Summary of composite score (LSR) by country and by visit: safety analysis set

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Table 3–23: Summary of composite score (LSR) by anatomical location and by visit: safety analysis set

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Table 3–24: Summary of visit of maximal intensity post baseline for composite score (LSR): safety analysis set

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<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
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<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Composite LSR score</td>
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<td></td>
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<tr>
<td>No scores higher</td>
<td>1</td>
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<td>0</td>
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</tr>
<tr>
<td>than baseline</td>
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<td></td>
<td></td>
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<td>Day 5</td>
<td>31</td>
<td>37</td>
<td>37</td>
<td>9</td>
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<tr>
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<td>18</td>
<td>11</td>
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</tr>
<tr>
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<td>0</td>
<td>3</td>
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</tr>
<tr>
<td>Day 31</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
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</tr>
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Table 3–25: Summary of visit of return to baseline for composite score (LSR): safety analysis set

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<th>Ingenol 2 days (n=55)</th>
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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Composite LSR score</td>
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<td></td>
<td></td>
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</tr>
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<td>5.1%</td>
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<td>0.0%</td>
<td>0</td>
<td>0.0%</td>
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<tr>
<td>Day 17</td>
<td>8</td>
<td>14.5%</td>
<td>7</td>
<td>11.9%</td>
</tr>
<tr>
<td>Day 31</td>
<td>19</td>
<td>34.5%</td>
<td>20</td>
<td>33.9%</td>
</tr>
<tr>
<td>Day 56</td>
<td>17</td>
<td>30.9%</td>
<td>20</td>
<td>33.9%</td>
</tr>
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<td>18.2%</td>
<td>9</td>
<td>15.3%</td>
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<td>Total</td>
<td>55</td>
<td>100.0%</td>
<td>59</td>
<td>100.0%</td>
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</tbody>
</table>

1) 5 subjects had maximum value at Day 56 and the remaining subjects had 1 to 3 composite LSR units from a return to baseline: 27 subjects: 1 unit; 4 subjects: 2 units; and 1 subject: 3 units.
Table 3–26: Summary of burning sensation by day: safety analysis set

<table>
<thead>
<tr>
<th>Day</th>
<th>Burning sensation</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Day 1</td>
<td>No burning</td>
<td>50</td>
<td>90.9</td>
<td>53</td>
<td>89.8</td>
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<tr>
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<td>4</td>
<td>7.3</td>
<td>6</td>
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<tr>
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<td>Uncomfortable burning</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
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<td>Very uncomfortable burning</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
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<td>Total</td>
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<td>100.0</td>
<td>59</td>
<td>100.0</td>
</tr>
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<td>89.1</td>
<td>22</td>
<td>37.3</td>
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<td>9.1</td>
<td>22</td>
<td>37.3</td>
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<td>Uncomfortable burning</td>
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<td>1.8</td>
<td>11</td>
<td>18.6</td>
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<td>Very uncomfortable burning</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
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<td>0.0</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
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<td>Total</td>
<td>55</td>
<td>100.0</td>
<td>59</td>
<td>100.0</td>
</tr>
<tr>
<td>Day 3</td>
<td>No burning</td>
<td>15</td>
<td>27.3</td>
<td>15</td>
<td>26.3</td>
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<tr>
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<td>29</td>
<td>50.9</td>
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<tr>
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<td>11</td>
<td>19.3</td>
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<td>5.5</td>
<td>1</td>
<td>1.8</td>
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<td>0.0</td>
<td>1</td>
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Continued...
Table 3-26: Summary of burning sensation by day: safety analysis set (continued)

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<th>Day</th>
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<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<td>n¹</td>
<td>%</td>
</tr>
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<td>3.6</td>
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<td>1.8</td>
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1) n=Number of subjects
Table 3–27: Summary of time to onset by burning sensation and by day: safety analysis set

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<th>Burning Sensation</th>
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<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<tr>
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<td></td>
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</tr>
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Table 3-27: Summary of time to onset by burning sensation and by day: safety analysis set (continued)

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<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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<tbody>
<tr>
<td>Uncomfortable burning</td>
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</tr>
<tr>
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Table 3-27: Summary of time to onset by burning sensation and by day: safety analysis set (continued)

<table>
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<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
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<td>Mean (hours)</td>
<td>Mean (hours)</td>
<td>Mean (hours)</td>
</tr>
<tr>
<td></td>
<td>n=55</td>
<td>n=59</td>
<td>n=49</td>
<td>n=61</td>
</tr>
<tr>
<td>Very uncomfortable burning</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
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<td></td>
</tr>
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</tr>
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<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

|                            |                        |                        |                        |                        |
|                            | 0.36                   | 1.65                   | 1.00                   | 0.52                   |
|                            | 0.33                   | 0.29                   | 0.00                   | 0.04                   |
|                            | 0.5                    | 0.0                    | 2.0                    | 2.0                    |
|                            | 3                      | 4                      | 4                      | 4                      |

24NOV14:08:31:04 LP0105 1020 t26 time by sense.doc

Continued...
Table 3-27: Summary of time to onset by burning sensation and by day: safety analysis set (continued)

<table>
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<tr>
<th>Burning Day Onset (hours)</th>
<th>Ingenol 2 days (n=55)</th>
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Table 3–28: Summary of duration by burning sensation and by day: safety analysis set

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Table 3-28: Summary of duration by burning sensation and by day: safety analysis set (continued)

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Table 3-28: Summary of duration by burning sensation and by day: safety analysis set (continued)

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Table 3-28: Summary of duration by burning sensation and by day: safety analysis set (continued)

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Table 3-28: Summary of duration by burning sensation and by day: safety analysis set (continued)

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Table 3–29: Maximum burning sensation: safety analysis set

<table>
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<tr>
<th>Maximal Burning</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
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<td>United States</td>
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<td>2</td>
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<td>1</td>
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<td>3</td>
<td>8</td>
<td>0</td>
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<tr>
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<tr>
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<td>Total</td>
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Table 3-29: Maximum burning sensation: safety analysis set (continued)

<table>
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<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Number of subjects</td>
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<td>Number of subjects</td>
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<td>No burning</td>
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<tr>
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<td>0.0</td>
<td>4</td>
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**Table 3–30: Regression analysis of global satisfaction (TSQM) versus maximal burning: safety analysis set**

<table>
<thead>
<tr>
<th>TSQM vs burning</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
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</thead>
<tbody>
<tr>
<td>Spearman rank correlation</td>
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<tr>
<td>p-value</td>
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<td>0.71</td>
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1) 55, 58 and 47 subjects contributed data in Ingenol 2 days, 3 days and 4 days respectively.
Table 3–31: Regression analysis of global satisfaction (TSQM) versus maximal duration for the two high levels combined: safety analysis set

<table>
<thead>
<tr>
<th>TSQM vs burning</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
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<td>p-value</td>
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<td>0.83</td>
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1) 6, 6 and 9 subjects contributed data in Ingenol 2 days, 3 days and 4 days respectively
Table 3–32: Vital signs by visit: safety analysis set

<table>
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<tr>
<th>Vital signs by visit</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Diastolic Blood Pressure (mmHg)</td>
<td></td>
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</tr>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>76.2</td>
<td>75.1</td>
<td>76.5</td>
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<tr>
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<td>9.9</td>
<td>10.1</td>
<td>10.4</td>
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<tr>
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<td><strong>Systolic Blood Pressure (mmHg)</strong></td>
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Table 3-32: Vital signs by visit: safety analysis set (continued)

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<td>49</td>
<td>61</td>
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<td><strong>Day 56</strong></td>
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Table 3–33: Change in vital signs from baseline to Week 8: safety analysis set

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<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
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</thead>
<tbody>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
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</tr>
<tr>
<td>Mean</td>
<td>1.0</td>
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</tr>
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<td>57</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
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<td>Minimum</td>
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<td>-70</td>
<td>-44</td>
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<td>28</td>
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<td>Number</td>
<td>54</td>
<td>58</td>
<td>48</td>
<td>57</td>
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Table 3–34: Summary of Haematology parameters and change from baseline by visit: safety analysis set

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Table 3-34: Summary of Haematology parameters and change from baseline by visit: safety analysis set (continued)

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### Table 3-34: Summary of Haematology parameters and change from baseline by visit: safety analysis set (continued)

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Table 3-34: Summary of Haematology parameters and change from baseline by visit: safety analysis set (continued)

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### Table 3-34: Summary of Haematology parameters and change from baseline by visit: safety analysis set (continued)

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Table 3-34: Summary of Haematology parameters and change from baseline by visit: safety analysis set (continued)

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Table 3-34: Summary of Haematology parameters and change from baseline by visit: safety analysis set (continued)

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Table 3-34: Summary of Haematology parameters and change from baseline by visit: safety analysis set (continued)

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Table 3-34: Summary of Haematology parameters and change from baseline by visit: safety analysis set (continued)

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## Table 3–35: Summary of Biochemistry parameters and change from baseline by visit:
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Table 3-35: Summary of Biochemistry parameters and change from baseline by visit: safety analysis set (continued)

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Table 3-35: Summary of Biochemistry parameters and change from baseline by visit: safety analysis set (continued)

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Table 3-35: Summary of Biochemistry parameters and change from baseline by visit: safety analysis set (continued)

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Table 3-35: Summary of Biochemistry parameters and change from baseline by visit: safety analysis set (continued)

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Table 3-35: Summary of Biochemistry parameters and change from baseline by visit: safety analysis set (continued)

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Table 3-35: Summary of Biochemistry parameters and change from baseline by visit: safety analysis set (continued)

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Table 3–36: Concomitant medication started during trial inside treatment area

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<td>No. Drugs</td>
</tr>
<tr>
<td>Antiinfectives for systemic use</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Dermatologicals</td>
<td>2</td>
<td>2</td>
<td>3.6</td>
<td>10</td>
</tr>
<tr>
<td>Nervous system</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
</tr>
<tr>
<td>Various</td>
<td>6</td>
<td>6</td>
<td>10.9</td>
<td>9</td>
</tr>
<tr>
<td>Total number of drugs taken²</td>
<td>9</td>
<td>22</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Total number of subjects taking drugs</td>
<td>8</td>
<td>14.5</td>
<td></td>
<td>14</td>
</tr>
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</table>

1) Drugs/procedures with the same Anatomical Therapeutic Chemical (ATC) classification level 4 code and generic name/preferred term name which have been taken by the same subject have been counted.
Table 3–37: Concurrent procedures started during trial inside treatment area

<table>
<thead>
<tr>
<th>Concomitant procedure name</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Proc</td>
<td>No. Subj</td>
<td>%</td>
<td>No. Proc</td>
</tr>
<tr>
<td>Aerobic bacterial culture</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Biopsies X 2</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Biopsy</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Biopsy (shave) - left inner forearm</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Biopsy (shave) - left outer forearm</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Biopsy of left dorsal hand</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Biopsy of lesion left arm</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Culture-In treatment area</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Curettage</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Curettage X 2</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Curette - left arm</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Curette and cautery right forearm</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Drained blisters-left arm in treatment area</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Excision SCC X 2 in treatment area</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Excision lesion dorsum right hand</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Excision lesion right forearm</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Excision of ? SCC on right forearm</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Excision of SCC left wrist</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
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</tbody>
</table>
Table 3-37: Concurrent procedures started during trial inside treatment area (continued)

<table>
<thead>
<tr>
<th>Concomitant procedure name</th>
<th>Ingenol 2 days (n=55)</th>
<th>Ingenol 3 days (n=59)</th>
<th>Ingenol 4 days (n=49)</th>
<th>Vehicle (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excision of lesion left arm</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Excision right shin</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Excisional biopsy - left forearm</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Liquid nitrogen to ak</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>left forearm, within</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punch biopsy - left</td>
<td>1</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>forearm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punch biopsy right shin</td>
<td>1</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Shave biopsy left</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>lateral leg</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Shave biopsy left anterior shin</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Swab for m/c/s</td>
<td>1</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
</tr>
<tr>
<td>Swab on right forearm</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total number of procedures</strong></td>
<td><strong>9</strong></td>
<td></td>
<td></td>
<td><strong>9</strong></td>
</tr>
<tr>
<td><strong>Total number of subjects</strong></td>
<td><strong>7</strong></td>
<td>12.7</td>
<td></td>
<td><strong>8</strong></td>
</tr>
</tbody>
</table>

24NOV14:08:32:18 LP0105 1020 t36_cp_in_trt_area.doc
Table 3–38: Neoplasm adverse events in the treatment area

<table>
<thead>
<tr>
<th>Site</th>
<th>Subject N°</th>
<th>Treatment anatomical location</th>
<th>Skin type</th>
<th>Duration of AK (years)</th>
<th>Previous skin cancer</th>
<th>Lesions at cancer baseline</th>
<th>Preferred term</th>
<th>Lowest level term</th>
<th>Severity/intensity</th>
<th>Causality</th>
<th>Serious</th>
<th>Outcome</th>
<th>Study day of start of AE</th>
<th>Study day of end of AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>44</td>
<td>Ingenol 2 days</td>
<td>Y</td>
<td>20</td>
<td>Bowen's disease</td>
<td>Intraepidermal carcinoma</td>
<td>Moderate</td>
<td>Not Related</td>
<td>N</td>
<td>RECOVERED</td>
<td>63/78</td>
<td>63/78</td>
<td>30JUN15:14:22:33 LP0105-1020 t49 list1.doc</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>/Arm not including back of hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Ingenol 2 days</td>
<td>Y</td>
<td>6</td>
<td>Squamous cell carcinoma of skin</td>
<td>Squamous cell carcinoma of skin</td>
<td>Severe</td>
<td>Possible</td>
<td>Y</td>
<td>RECOVERED</td>
<td>49/77</td>
<td>49/77</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>/Arm included back of hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Ingenol 2 days</td>
<td>N</td>
<td>12</td>
<td>Squamous cell carcinoma of skin</td>
<td>Squamous cell carcinoma of skin</td>
<td>Moderate</td>
<td>Possible</td>
<td>Y</td>
<td>RECOVERED</td>
<td>35/71</td>
<td>35/71</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>/Arm including back of hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>14</td>
<td>Ingenol 3 days</td>
<td>Y</td>
<td>18</td>
<td>Squamous cell carcinoma of skin</td>
<td>Squamous cell carcinoma of skin in situ</td>
<td>Moderate</td>
<td>Not Related</td>
<td>Y</td>
<td>RECOVERED</td>
<td>33/88</td>
<td>33/88</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>/Arm including back of hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Ingenol 3 days</td>
<td>N</td>
<td>8</td>
<td>Squamous cell carcinoma of skin</td>
<td>Squamous cell carcinoma of skin in situ</td>
<td>Moderate</td>
<td>Possible</td>
<td>Y</td>
<td>RECOVERED</td>
<td>54/72</td>
<td>54/72</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>/Arm including back of hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Ingenol 3 days</td>
<td>Y</td>
<td>7</td>
<td>Squamous cell carcinoma of skin</td>
<td>Squamous cell carcinoma of skin</td>
<td>Mild</td>
<td>Related</td>
<td>Y</td>
<td>RECOVERED</td>
<td>33/76</td>
<td>33/76</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>/Arm not including back of hand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Continued...
Table 3-38: Neoplasm adverse events in the treatment area

<table>
<thead>
<tr>
<th>Site subject N°</th>
<th>Treatment anatomical location</th>
<th>Skin type</th>
<th>Duration of AK (years)</th>
<th>Previous skin cancer at baseline</th>
<th>Preferred term</th>
<th>Number of AK lesions at baseline</th>
<th>Lowest level term</th>
<th>Severity/intensity</th>
<th>Causality</th>
<th>Severity</th>
<th>Outcome</th>
<th>Study day of start of AE</th>
<th>Study day of end of AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingenol 4 days</td>
<td>/Leg</td>
<td>I</td>
<td>39</td>
<td>Y</td>
<td>9</td>
<td>Seborrheic keratosis</td>
<td>Seborrheic keratosis</td>
<td>Mild</td>
<td>Not</td>
<td>N</td>
<td>RECOVERED/RESOLVED</td>
<td>50/64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/Arm not including back of hand</td>
<td>I</td>
<td>28</td>
<td>Y</td>
<td>18</td>
<td>Keratoacanthoma</td>
<td>Keratoacanthoma</td>
<td>Moderate</td>
<td>Possible</td>
<td>N</td>
<td>RECOVERED/RESOLVED</td>
<td>30/60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/Arm including I back of hand</td>
<td>I</td>
<td>19</td>
<td>Y</td>
<td>15</td>
<td>Keratoacanthoma</td>
<td>Keratoacanthoma</td>
<td>Moderate</td>
<td>Possible</td>
<td>Y</td>
<td>RECOVERED/RESOLVED</td>
<td>26/57</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/Arm including I back of hand</td>
<td>I</td>
<td>5</td>
<td>Y</td>
<td>13</td>
<td>Squamous cell carcinoma of skin</td>
<td>Squamous cell carcinoma of skin</td>
<td>Severe</td>
<td>Possible</td>
<td>Y</td>
<td>RECOVERED/RESOLVED</td>
<td>31/39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/Arm not including back of hand</td>
<td>I</td>
<td>0</td>
<td>Y</td>
<td>6</td>
<td>Seborrheic keratosis</td>
<td>Seborrheic keratosis</td>
<td>Mild</td>
<td>Possible</td>
<td>N</td>
<td>RECOVERED/RESOLVED</td>
<td>19/85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>/Arm not including back of hand</td>
<td>I</td>
<td>0</td>
<td>Y</td>
<td>6</td>
<td>Squamous cell carcinoma of skin</td>
<td>Squamous cell carcinoma of skin</td>
<td>Mild</td>
<td>Possible</td>
<td>Y</td>
<td>RECOVERED/RESOLVED</td>
<td>19/85</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3-1: Plot of maximum individual and composite LSR score by treatment group

![Bar chart showing mean maximal LSR scores for different symptoms and treatment groups.](image-url)
Figure 3-2: Mean of composite LSR score versus time by treatment group

![Graph showing the mean composite LSR score over time for different treatment groups. The x-axis represents day, and the y-axis represents composite LSR score. The graph includes lines for Vehicle, Ingenol 2 days, Ingenol 3 days, and Ingenol 4 days. Week 4 is highlighted on the graph.]
Figure 3-3: Plot LSR category scores versus time by treatment group
Figure 3-4: Plot burning category versus time by treatment group

Figure 3-5: Maximal burning category by treatment group
Figure 3-6: Global satisfaction (TSQM) versus maximal burning sensation
Figure 3-7: Global satisfaction (TSQM) versus maximal duration – two low levels of burning combined
Figure 3-8: Global satisfaction (TSQM) versus maximal duration – two high levels of burning combined
0 End-of-Text Listings

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Treatment group=Ingenol 3 days ...................................................................................424
Treatment group=Ingenol 4 days ...................................................................................425
<table>
<thead>
<tr>
<th>Centre/Subject ID</th>
<th>Location</th>
<th>Preferred term/Reported term</th>
<th>Start/Stop</th>
<th>Duration (days)</th>
<th>Relation</th>
<th>Intensity</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>APPLICATION SITE PAIN/Burning at treatment site</td>
<td>PPD</td>
<td>5</td>
<td>Probable</td>
<td>Moderate</td>
<td>Ip discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
<tr>
<td>PPD</td>
<td>Other skin area</td>
<td>ECZEMA/Auto-Eczematization reaction</td>
<td>PPD</td>
<td>14</td>
<td>Probable</td>
<td>Moderate</td>
<td>Ip discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
</tbody>
</table>

04JUN2015:13:32:42 Programs-Listings ae(where=aecn='None')
<table>
<thead>
<tr>
<th>Centre/Subject ID</th>
<th>Location</th>
<th>Preferred term/Reported term</th>
<th>Start/Stop</th>
<th>Duration (days)</th>
<th>Relation</th>
<th>Intensity</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>APPLICATION SITE PAIN/ Lsr-Pain</td>
<td>PPD / PPD</td>
<td>11</td>
<td>Probable</td>
<td>Severe</td>
<td>Discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>APPLICATION SITE PAIN/ Burning</td>
<td>PPD / PPD</td>
<td>14</td>
<td>Probable</td>
<td>Severe</td>
<td>Discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>APPLICATION SITE PAIN/ Severe allergic reaction</td>
<td>PPD / PPD</td>
<td>10</td>
<td>Probable</td>
<td>Moderate</td>
<td>Discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>APPLICATION SITE INFECTION/ Beta - streptococcus, group b</td>
<td>PPD / PPD</td>
<td>9</td>
<td>Possible</td>
<td>Moderate</td>
<td>Discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>APPLICATION SITE PAIN/ Burning</td>
<td>PPD / PPD</td>
<td>6</td>
<td>Possible</td>
<td>Severe</td>
<td>Discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>APPLICATION SITE PAIN/ Pain secondary to burning</td>
<td>PPD / PPD</td>
<td>6</td>
<td>Possible</td>
<td>Severe</td>
<td>Discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>APPLICATION SITE PAIN/ Burning</td>
<td>PPD / PPD</td>
<td>3</td>
<td>Possible</td>
<td>Moderate</td>
<td>Discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>APPLICATION SITE PAIN/ Pain</td>
<td>PPD / PPD</td>
<td>13</td>
<td>Possible</td>
<td>Moderate</td>
<td>Discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>APPLICATION SITE INFECTION/ Infection</td>
<td>PPD / PPD</td>
<td>15</td>
<td>Possible</td>
<td>Moderate</td>
<td>Discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
</tbody>
</table>
### Listing 0-2: Subjects Withdrawn from treatment due to AE

**Treatment group=Ingenol 4 days**

<table>
<thead>
<tr>
<th>Centre/Subject ID</th>
<th>Location</th>
<th>Preferred term/Reported term</th>
<th>Start/Stop</th>
<th>Duration (days)</th>
<th>Relation</th>
<th>Intensity</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>/ Inside ak treatment area</td>
<td>APPLICATION SITE PAIN/ Burning</td>
<td>/</td>
<td>8</td>
<td>Probable</td>
<td>Severe</td>
<td>Ip discontinued</td>
<td>Recovered</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>/ Inside ak treatment area</td>
<td>APPLICATION SITE PAIN/ Burning heat</td>
<td>/</td>
<td>5</td>
<td>Probable</td>
<td>Severe</td>
<td>Ip discontinued</td>
<td>Recovered</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>/ Inside ak treatment area</td>
<td>APPLICATION SITE PAIN/ Pain</td>
<td>/</td>
<td>4</td>
<td>Probable</td>
<td>Severe</td>
<td>Ip discontinued</td>
<td>Recovered</td>
<td>No</td>
<td></td>
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</table>

04JUN2015:13:32:42 Programs=Listings ae(where=aeacn='None')
### Listing 0-2: Subjects Withdrawn from treatment due to AE

**Treatment group=Vehicle**

<table>
<thead>
<tr>
<th>Centre/Subject ID</th>
<th>Location</th>
<th>Preferred term/Reported term</th>
<th>Start/Stop</th>
<th>Duration (days)</th>
<th>Relation</th>
<th>Intensity</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td>Non-Cutaneous</td>
<td>PNEUMONIA/Pneumonia r upper &amp; middle lobe</td>
<td>04JUN2015:13:32:42</td>
<td>23</td>
<td>Not related</td>
<td>Moderate</td>
<td>Discontinued</td>
<td>Recovered</td>
<td>No</td>
</tr>
</tbody>
</table>

04JUN2015:13:32:42 Programs--Listings ae(where=aeacc='None')
## Listing 0-3: Deaths

<table>
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<tr>
<th>Date of program execution</th>
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<tbody>
<tr>
<td>18DEC2014:14:28:22</td>
<td>No data for this listing</td>
</tr>
</tbody>
</table>

18DEC2014:14:28:22  Programs-Listings  ae(where=upcase(aeout)='FATAL')
### Listing 0-4: Serious Adverse Events  
**Treatment group=Ingenol 2 days**

<table>
<thead>
<tr>
<th>Centre/Subject ID</th>
<th>Location</th>
<th>Preferred term/Reported term</th>
<th>Start/Stop</th>
<th>Duration (days)</th>
<th>Relation</th>
<th>Intensity</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>SQUAMOUS CELL CARCINOMA OF SKIN/</td>
<td>PPD</td>
<td>22</td>
<td>Possible</td>
<td>Severe</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sqaumous cell carcinomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>SQUAMOUS CELL CARCINOMA OF SKIN/</td>
<td>PPD</td>
<td>29</td>
<td>Possible</td>
<td>Moderate</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCC right shin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>SQUAMOUS CELL CARCINOMA OF SKIN/</td>
<td>PPD</td>
<td>37</td>
<td>Not</td>
<td>Mild</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Squamous cell carcinoma IN situ lt. forearm</td>
<td></td>
<td></td>
<td>related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Listing 0-4: Serious Adverse Events
**Treatment group=Ingenol 3 days**

<table>
<thead>
<tr>
<th>Centre/Subject ID</th>
<th>Location</th>
<th>Preferred term/Reported term</th>
<th>Start/Stop</th>
<th>Duration (days)</th>
<th>Relation</th>
<th>Intensity</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td>Non-Cutaneous</td>
<td>ANGINA PECTORIS/Angina</td>
<td>PPD</td>
<td>3</td>
<td>Not related</td>
<td>Moderate</td>
<td>None</td>
<td>Recovered with sequelae</td>
<td>Yes</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>SQUAMOUS CELL CARCINOMA OF SKIN/SCC IN treatment area - dorsum right hand</td>
<td>PPD</td>
<td>1</td>
<td>Possible</td>
<td>Moderate</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>SQUAMOUS CELL CARCINOMA OF SKIN/SCC IN treatment site right forearm</td>
<td>PPD</td>
<td>1</td>
<td>Possible</td>
<td>Moderate</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>SQUAMOUS CELL CARCINOMA OF SKIN/SCC of the skin</td>
<td>PPD</td>
<td>35</td>
<td>Possible</td>
<td>Moderate</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>SQUAMOUS CELL CARCINOMA OF SKIN/SCC left wrist</td>
<td>PPD</td>
<td>19</td>
<td>Not related</td>
<td>Moderate</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
<tr>
<td>PPD</td>
<td>Inside ak treatment area</td>
<td>SQUAMOUS CELL CARCINOMA OF SKIN/SCC</td>
<td>PPD</td>
<td>44</td>
<td>Possible</td>
<td>Mild</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Listing 0-4: Serious Adverse Events

**Treatment group=Iangenol 4 days**

<table>
<thead>
<tr>
<th>Centre/Subject ID</th>
<th>Location</th>
<th>Preferred term/Reported term</th>
<th>Start/Stop</th>
<th>Duration (days)</th>
<th>Relation</th>
<th>Intensity</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD / PPD</td>
<td>Inside ak treatment area</td>
<td>SQUAMOUS CELL CARCINOMA OF SKIN/SCC of the skin</td>
<td>PPD / PPD</td>
<td>31</td>
<td>Possible</td>
<td>Severe</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
<tr>
<td>PPD / PPD</td>
<td>Inside ak treatment area</td>
<td>KERATOACANTHOMA/Keratoacanthoma</td>
<td>PPD / PPD</td>
<td>32</td>
<td>Possible</td>
<td>Moderate</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
<tr>
<td>PPD / PPD</td>
<td>Non-Cutaneous</td>
<td>RETINAL MELANOMA/Retinal melanoma</td>
<td>PPD / PPD</td>
<td>103</td>
<td>Not related</td>
<td>Severe</td>
<td>None</td>
<td>Recovered with sequelae</td>
<td>Yes</td>
</tr>
<tr>
<td>PPD / PPD</td>
<td>Inside ak treatment area</td>
<td>SQUAMOUS CELL CARCINOMA OF SKIN/Squamous cell carcinoma</td>
<td>PPD / PPD</td>
<td>9</td>
<td>Probable</td>
<td>Severe</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
<tr>
<td>PPD / PPD</td>
<td>Inside ak treatment area</td>
<td>SQUAMOUS CELL CARCINOMA OF SKIN/SCC</td>
<td>PPD / PPD</td>
<td>67</td>
<td>Possible</td>
<td>Mild</td>
<td>None</td>
<td>Recovered</td>
<td>Yes</td>
</tr>
</tbody>
</table>

18DEC2014:14:28:22 Programs:Listings $\text{as(first-uppercase(asser))='Y'}$
**ELECTRONIC SIGNATURES**

Electronic signature made within eDoc LEO by LEO Pharma A/S employees or employees of any LEO Pharma A/S affiliate located anywhere in the world, are to be considered to be legally binding equivalent of traditional handwritten signatures.

<table>
<thead>
<tr>
<th>Signed by</th>
<th>Meaning of Signature</th>
<th>Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td>PPD Biostatistics Approval</td>
<td>09-Jul-2015 16:25 GMT+020</td>
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<tr>
<td>PPD</td>
<td>PPD Approval</td>
<td>09-Jul-2015 16:53 GMT+020</td>
</tr>
</tbody>
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