PEP005 (Ingenol Mebutate) Gel

2.5 Clinical Overview for Actinic Keratosis

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Module 2
Clinical Overview
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1 PRODUCT DEVELOPMENT RATIONALE

1.1 ACTINIC KERATOSIS

Actinic keratosis (AK) is a common skin condition visible as thickened, cornified, scaly lesions and characterised histologically by atypical epithelial proliferation.(1) Actinic keratoses usually develop on areas that are frequently exposed to the sun (e.g., face, lips, ears, scalp, neck, forearms, and 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.(2,3) In addition to the emotional strain, AK lesions can be painful and easily traumatised causing bleeding.(3,4,5,6)

It is estimated that AK occurs in 11–50% of the population aged 40 and older in the United States (US) and Australia.(1) In Europe the prevalence rate is from 11-25% for people aged 40 or older.(7,8) Patients with AK tend to have Fitzpatrick type I or II skin (fair skin) which burns and does not tan.(5)

In the US and Australia, the majority of people who develop AK lesions have fair skin with Fitzpatrick skin types I and II.(9,10) The same is true for Northern European populations, such as the English, Irish, Scottish, and Scandinavians.(11)

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 evident by the presence of multiple subclinical and clinically visible AK lesions as well as multifocal preneoplastic changes with genetic mutations.(12) There is also increasing evidence that AK represents squamous cell carcinoma (SCC) in situ in its earliest stages.(1, 13,14) Histological evidence shows that contiguous AK is present in 97% of SCC lesions on sun-damaged skin.(13) Actinic keratosis is linked epidemiologically to development of SCC (15), and both conditions share specific gene expression.(16) If left untreated, AK may progress to SCC, with significant morbidity and death.(13)

1.2 CURRENT TREATMENT PRACTICE

Current treatment options for AK lesions consist of cryotherapy, photodynamic therapy, curettage, excisional surgery and topical products.

1.2.1 Lesion-Specific Treatment

Lesion-specific treatments include photodynamic therapy, cryotherapy, curettage, and excisional surgery. Photodynamic therapy and cryotherapy can be painful, and patients are often left with hypopigmented spotting where cryotherapy is applied.(17,18) Curettage (with or without electrosurgery) and excisional surgery are alternatives to cryosurgery.(19)

1.2.2 Topical Products for Field Treatment

Topical products include 5-fluorouracil (5-FU), diclofenac, and imiquimod, and are commonly used as field treatment for multiple lesions over larger skin areas. 5-Fluorouracil is approved in the US under the brand names of Efudex®, Fluoroplex®, and Carac® (20,21,22) and in Australia and the European Union (EU) under the brand name of Efudix®.(23,24) Diclofenac is approved in Australia and the US as Solaraze® and in some European countries as Solaraze™.(25,26,27) Imiquimod is approved in the US under the brand names of Aldara® (28) and Zyclara™ (29), in Australia under the brand name of Aldara™ (30), and the EU under the brand name of Aldara®.(31)

Two 5-FU products (Efudex®/Efudix® and Fluoroplex®) are approved without restriction to anatomical location.(20,21,23,24) Three studies are described where field treatment of 5-FU 1% or 5% cream was applied once or twice a day for approximately 2 to 8 weeks. One study suggested a complete clearance rate (no AK lesions in the treated area) of 40% (32) and the results from a second study indicated that no patients had complete clearance.(33) In a third study, complete clearance was not measured; the number of AK lesions was reported as a mean (± standard deviation) of 15.3 (± 6.9) at baseline and 4.2 (± 2.5) after 3 months.(34) One 5-FU product approved in the US (Carac®) is indicated for treatment on the face and scalp.(22) When Carac® is applied once daily for two to four weeks, complete clearance rates range from 15-58%.(22)

Diclofenac (Solaraze®) is marketed as a 3% gel and is approved for treatment without anatomical restriction, it requires twice daily application for 60-90 days, and complete clearance rates of 34-47% have been reported.(26)

Imiquimod is approved for treatment on the face and scalp, and is available in two strengths. The first is a 5% cream (Aldara™) which in Australia is approved for cyclic treatment; 3 times per week for 4 weeks. After a 4-week no-treatment period another 4-week course can be applied if required. A continuous treatment period of 3 times per week for 16 weeks is also approved in Australia (30). In the US Aldara® is approved for application twice weekly for

16 weeks; complete clearance rates range from 44-46%.(28) In Europe, the approved regimen is the same as the cyclic regimen approved in Australia. (31) The other strength is a 3.75% cream (Zyclara™) which is only approved in the US and is applied once daily before bedtime to the skin of the affected area (entire face or balding scalp) for two 2-week treatment cycles separated by a 2-week no-treatment period; complete clearance rates range from 26-46%.(29)

Measurable plasma concentrations have been documented with use of 5-FU, diclofenac, and imiquimod.(20,22,26,28,29) Irritation resulting from 5-FU treatment can be unsightly during and after therapy,(35) diclofenac has the potential to cause allergic reactions (36), and imiquimod, in addition to having significant local irritation, has been associated with systemic side effects, such as fatigue, flu-like symptoms, and angioedema.(28,37,38,39) Study medication discontinuation rates due to adverse events (AEs) (primarily skin irritation and application site reactions) during Phase 3 clinical trials have been reported to be 12% for 5-FU (22) and 18% for diclofenac.(26) For imiquimod, a rest period was required during treatment with Aldara® for 16% of patients due to local skin reactions and for 3% of patients due to treatment site infections; additionally, 2% of patients discontinued due to skin reactions.(28) With Zyclara™, 11% of patients required a rest period.(29) Lengthy treatment durations and adverse effects can reduce a patient's ability to complete a full course of therapy and can lead to treatment failure.(13)

1.3 PEP005 (INGENOL MEBUTATE) GEL

Ingenol mebutate is an ingenol derivative extracted from *Euphorbia peplus* L. (*E. peplus*), a member of the Spurge family. The sap of *E. peplus* has been used to treat a number of conditions including warts, corns, waxy growths, and skin cancer since the 1800s.(40,41,42) Results from an early proof of concept study using the crude sap of *E. peplus* (known as study PEP001) confirmed anecdotal community-based evidence of activity against AK and non-melanoma skin cancer (NMSC) when used topically. 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.(43) The mechanism of action in AK is not fully understood. 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) promoting an inflammatory response characterised as infiltration of neutrophils and other immunocompetent cells.(44,45,46,47,48,49,50) This mechanism of action distinguishes ingenol mebutate from current therapeutic options and provides a rationale for substantially shorter durations of treatment (two to three days) compared to approved topical AK products.

1.4 CLINICAL DEVELOPMENT PROGRAMME FOR PEP005 (INGENOL MEBUTATE) GEL

1.4.1 Advancement from Lesion-Specific Studies to Field Treatment Studies

The AK clinical development programme for PEP005 (ingenol mebutate) Gel explored varying treatment regimens for AK lesions located on the most common sun-exposed areas of the body. Early AK studies focused on treatment of individual AK lesions (i.e., lesion-specific therapy) (AGN 204332-004 and PEP005-001). Data from these early studies established the safety of PEP005 Gel when used as lesion specific therapy and allowed for further assessment of PEP005 Gel on a small field of skin (9 cm^2) containing a single target AK lesion in study PEP005-004. Subsequent studies used to determine optimal dosing for AK (PEP005-006, PEP005-007, PEP005-015) were conducted using field treatment application as well, except that the area treated was larger (i.e., a contiguous 25 cm^2 area) and contained multiple AK lesions (four to eight); these studies were more consistent with trials conducted with other topical products marketed for treatment of AK. Data from the AK studies also suggested that different concentrations and treatment regimens of PEP005 Gel would be needed to treat AK lesions depending on the anatomic location of the lesion (head versus non-head). Actinic keratosis lesions located on the face and scalp required lower concentrations applied for three days compared with AK lesions located on the non-head locations (trunk and extremities), which required higher concentrations of PEP005 Gel applied for only two days.

1.4.2 Choice of Vehicle Control Group for Adequate and Well-Controlled Studies

Based on the results of the Phase 2b dose ranging studies, two Phase 3 studies (PEP005-016 and PEP005-025) for the treatment of AK lesions on the head (face and scalp) and two Phase 3 studies (PEP005-014 and PEP005-028) for the treatment of AK lesions on non-head locations (trunk and extremities) were conducted. All four of these Phase 3 studies were randomised, controlled trials. A vehicle control was selected in these trials because it was considered the most appropriate choice to evaluate efficacy and safety.

A study design using an active comparator was not employed because of the potential to introduce bias with regard to the selection and timing of study endpoints. PEP005 Gel and any available active comparator used in the same patient population represent different modalities of treatment. As a result, efficacy endpoints would have been measured at different times during a comparator trial.

The duration of treatment for PEP005 Gel is 2 or 3 days with efficacy assessment at Day 57 following study medication application. Other products have longer durations of treatment, may require repeat treatment periods and take longer to achieve efficacy.. For 5-FU, at least 3 to 4 weeks is required for treatment, and efficacy assessment occurs at 12 weeks; imiquimod requires 4 weeks of treatment with efficacy assessment after the following 4-week off treatment period, or 16 weeks of continuous treatment (Aldara™); diclofenac requires 8 to 12 weeks of treatment and efficacy assessment at 16 weeks.(20,21,22,23,24,25, 26,27,28,29,30,31)

Therefore, the Applicant considered that an unbiased comparator trial would not be feasible.

1.4.3 Retreatment and Simultaneous Treatment Studies

No formal retreatment (repeat dosing) or simultaneous treatment studies were conducted in this clinical development programme. There were, however, 49 AK and non-AK patients who received multiple treatments with PEP005 Gel; these patients are discussed in the Overview of Safety (Section 5.5.7).

1.4.4 Histology Data

The majority of AKs are diagnosed clinically, not histologically. In clinical practice, biopsies are not routinely performed to identify AK lesions, particularly in cosmetically sensitive areas. However, a biopsy is warranted when malignancy is suspected. These diagnostic practices are well characterised in guidelines for AK management (51,52,53) and are associated with a high accuracy rate. In a study where 271 lesions were biopsied to correlate AK and SCC, clinical diagnosis and histopathologic findings agreed in 91% of the biopsies.(54) further supporting the appropriateness of a clinical diagnosis for AK.

Early in this clinical development programme, histological data were evaluated in a Phase 1, lesion-specific study (PEP005-001). Two single applications of study medication were applied directly to each selected lesion using PEP005 Gel at concentrations of 0.0025%, 0.01%, 0.05%, or vehicle gel. Punch biopsy samples were obtained pre-treatment to confirm the presence of AK, and post-treatment on Day 85 to determine lesion clearance. All biopsies were reviewed by a central dermatopathologist. Results showed absence of AK lesions on post-treatment biopsy for approximately 50% of the biopsies performed across all treatment groups. Although based on few patients these findings provide evidence of histological clearance.

Historically, lesion-specific therapy is the most common treatment for single lesions and hyperkeratotic AKs but it does not address multiple AK lesions in an area of photodamaged skin typical of field cancerisation.(12) Photodamaged fields contain preneoplastic changes, subclinical AKs, and clinically visible lesions. As this clinical development programme advanced to Phase 2 and 3 studies, the objectives focused on treating a field of skin containing multiple AK lesions instead of single lesions; clinical confirmation of clearance (instead of histological) is a standard efficacy measure and was used for this development programme. In the context of field cancerisation, obtaining post-treatment biopsies has the potential to provide even more ambiguity because the dysplastic changes are not homogenous over the total field. The extent of dysplasia of the field cannot be assessed with a single or even several biopsies. Post treatment biopsy within a photodamaged field is therefore not used as standard practice to confirm clearance of AK lesions.

Most of the adequate and well-controlled studies in this development programme evaluated field treatment in cosmetically sensitive treatment areas, such as the face, scalp, back of hand, or arm. Obtaining biopsies in cosmetically sensitive treatment areas introduces the risk of permanent scarring, which was another reason for not collecting histological data in the Phase 2 and 3 studies of this clinical programme.

1.4.5 Sample Size of Long Term Follow-Up Studies

Approximately 485 patients have received the “to be” marketed dose of 0.05% for 2 days (AK lesions on the trunk and extremities) and approximately 298 patients have received the “to be” marketed dose of 0.015% for 3 days (AK lesions on the face or scalp). In addition, approximately 200 patients with BCC, SCC or AK have been exposed to PEP005 Gel as lesion specific therapy and 332 subjects have been exposed to PEP005 Gel as part of establishing the topical safety of this compound. PEP005 Gel is well tolerated with most AEs being mild to moderate in severity and transient in nature.

Three long term observational studies were included in this clinical development programme (PEP005-030, PEP005-031, and PEP005-032) to evaluate safety and AK lesion recurrence. These three studies enrolled approximately 200 patients who achieved complete clearance at Day 57 in four Phase 3 studies. Of these patients, approximately half had lesions on the face and scalp and half had lesions on the trunk and extremities.

In order to ensure that the number of patients being followed long term was adequate, calculations were carried out to address the size of the current safety database with PEP005 Gel treated patients (i.e., a total of more than 1500 patients treated with one course of PEP005

and observed for 8 weeks with approximately 200 patients observed for up to 1 additional year [8 weeks plus 12 months]).

The upper limit of an exact two-sided 95% confidence interval for the probability of observing a specific adverse event, when 0 out of 1500 events has been observed, is 0.2% assuming a binomial distribution. Likewise the upper limit of an exact two-sided 95% confidence interval for the probability of observing a specific adverse event, when 0 out of 200 possible events has been observed, is 1.8%. In conclusion, the detectable frequency of adverse drug reactions observed within the short term is 0.2% and the detectable frequency of adverse drug reactions observed within a longer period of time is 1.8%.

The Applicant believes that the short duration of treatment with PEP005 Gel (2 consecutive days for AK lesions on the trunk or extremities and 3 consecutive days for AK lesions located on the face or scalp) together with the lack of systemic absorption of this compound with topical application, support the adequacy of the size of the safety database including the data on long term safety. Treatment with PEP005 Gel is acute in nature and a safety database of over 1000 patients is consistent with ICH E1A guidelines.

In addition, the clinical pattern of usage anticipated for treatment of AK with PEP005 Gel is estimated to be 2.5 times annually.(55) With a treatment pattern of 2.5 times annually, a patient's exposure to PEP005 Gel is not consistent with ICH S1A Guidelines (March 1995) definitions for chronic use (chronic or repeated intermittent use for longer than 6 months). The pattern of usage in Australia is expected to be similar.

Therefore, the Applicant considered the sample size in the long term observational studies adequate.

1.4.6 Duration of Long Term Follow-Up Studies

The Applicant considered several features regarding duration of follow-up, ability to assess long term safety in an adequately controlled study and published data from other long term follow-up studies in AK patients assessing recurrence. Published data regarding behaviour of patients with NMSC was also considered a factor in the design of the long-term follow-up studies.

Ten studies have been published with long term follow-up data in patients receiving field therapy for AK lesions (35,56,57,58,59,60,61,62,63,64) and 7 long term studies have been published in patients receiving PDT (lesion specific treatment).(65,66,67,68,69,70,71) These

studies range in duration of 3 months to 4 years. The definition of recurrence is not consistent across studies and results are reported anywhere from no recurrence (64) up to recurrence of 61.5%.(62) While a 4 year study is included here, it should be noted that this study only reported data in 4 patients and may point to the difficulty in following patients for extended periods. In general, these studies suggest that the most common duration of follow-up is 12 months. While shorter and longer duration studies are published (63), the most relevant studies for consideration in duration of follow-up for the PEP005 Gel programme are the prospective Phase 3 follow-up studies conducted with durations ranging from 12–18 months.(56,57,58) In addition to these, a 3 year follow-up study is being conducted in patients receiving imiquimod as a post-marketing approval commitment; results have not yet been published.

Published results from other studies suggest that the longer the follow-up period is for an observational study of AK lesions, the more potential there is for data to be confounded by spontaneous regression of AK lesions and in ability to control patient behaviour. In one epidemiological study data indicate that within a 12-month period, spontaneous remission may occur in 25% of AK lesions and that lesion remission is most frequently seen in patients who reduce their sun exposure.(72,73) However, even after excision of a NMSC and counselling about sun protection, noncompliance with sun exposure has been reported to be 38%.(74) Data beyond one year may represent recurrence rates observed in the general population but are not believed to represent true recurrence rates following treatment with PEP005 Gel in these patients due to influence from other external factors.

Evidence of SCC transformation is also difficult to define in published data. Long term follow-up studies which do provide data in AK patients do not generally report SCC transformation occurrence. Transformation of an AK lesion to SCC has been predicted to be <1:1000.(72) When AK patients were monitored for SCC transformation, data showed 60% of the SCCs arose from an AK identified in the past year and 40% arose from skin that was noted to be clinically normal in the past year.(75) Although these data help characterize the transformation of SCC in patients with AKs, they do not provide insight into the risk of developing SCC in a field of skin where AK lesions have completely cleared. To date, data have not been published which estimate the incidence of SCCs occurring in a field of skin that has been cleared of AK lesions.

After considering these factors, a follow-up period of 12 months was selected for each of the long-term studies, which is consistent with the follow-up period for other topical products,

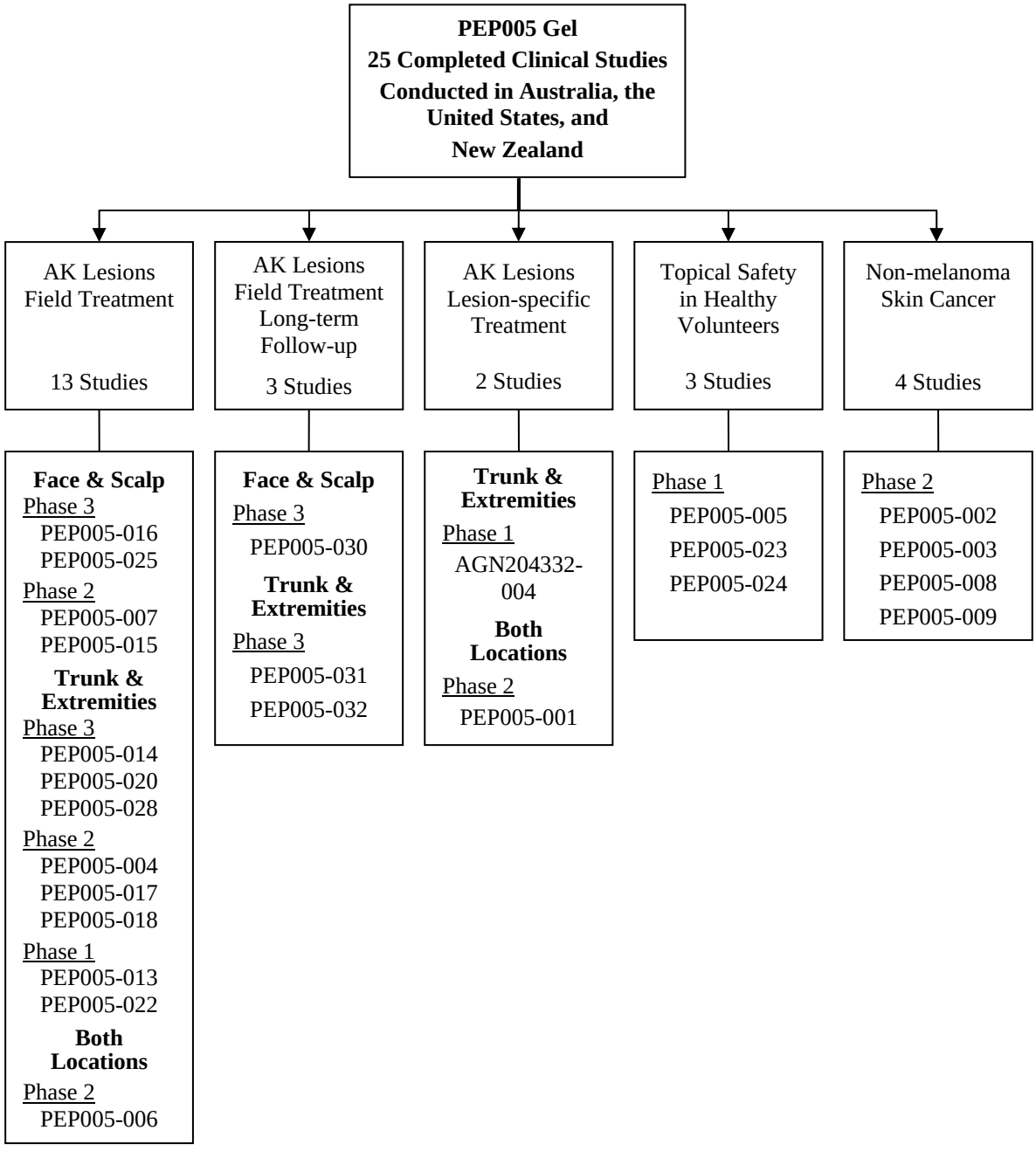
such as imiquimod, 5-FU, and diclofenac.(56,61,64)

1.4.7 Summary

To date, 25 clinical studies (Figure 1) have been completed and a total of 1774 patients/subjects in Australia, the United States, and New Zealand have received PEP005 Gel. All clinical studies were conducted in full conformance with the principles of International Conference on Harmonization (ICH) (ICH E6 1997) Good Clinical Practice (GCP) and the Declaration of Helsinki (1964 as amended in Seoul [2008]). Of these 25 completed studies, 18 were conducted in patients with AK. The remaining 7 studies contribute data to the safety profile of PEP005 Gel and included 3 topical safety studies performed in healthy volunteers and 4 safety studies in patients with NMSC.

As of 31 March 2011, a number of studies are ongoing or planned, including development activities in seborrheic keratosis and photo-damaged skin.

Figure 1: Overview of Completed Clinical Studies for PEP005 Gel



2 OVERVIEW OF BIOPHARMACEUTICS

PEP005 Gel is applied topically and not absorbed systemically.

3 OVERVIEW OF CLINICAL PHARMACOLOGY

Pre-clinical and clinical studies have shown that ingenol mebutate, at the concentrations applied topically for treatment of AK lesions, has no detectable systemic absorption. Results from both the in vitro and in vivo studies in humans demonstrated very little if any skin penetration of ingenol mebutate or its acyl isomers PEP015 or PEP025 into the systemic circulation following topical dosing of PEP005 Gel.

In in vitro metabolic studies, radiolabeled ingenol mebutate was found to be relatively metabolically stable in both whole blood and skin homogenates. In both tissues there was some hydrolysis to yield ingenol, but this generally accounted for less than 1% of the radioactivity.

The human PK profile of topical application of PEP005 Gel was predicted using allometric scaling from in vivo animal PK and in vitro percutaneous absorption data. Based on the estimated ingenol mebutate blood clearance V_{ss}, assumed absorption rate constant, and topical bioavailability, the maximum intended clinical dose (2 µg/kg/day) would not produce measurable systemic blood levels of ingenol mebutate. Assuming linear PK, it is predicted that a minimal topical dose of 2000 µg/kg/day would be required to produce systemic C_{max} ingenol mebutate concentrations above the LLOQ (0.1 ng/mL) of the established bioanalytical assay. This quantity of drug is far in excess of possible clinical usage.

Pharmacokinetic samples were collected from a total of 32 patients (25 on PEP005 Gel and 7 on vehicle) enrolled in four independent PEP005 Gel clinical studies for the treatment of non-head AK lesions [AGN 204332-004, PEP005-004, PEP005-013, PEP005-017]. The highest concentration and treatment area evaluated was 0.05 µg/mm^2 of PEP005 Gel, 0.05% applied once daily to a 100 cm^2 area for two consecutive days [PEP005-013 and PEP005-017]. No systemic levels of ingenol mebutate or its two isomers, PEP015 and PEP025, were quantifiable in any of the blood samples collected for PK analysis (i.e., concentrations were below the LLOQ).

No clinical metabolism studies have been performed to date because ingenol mebutate shows no systemic absorption when administered topically. However, in vitro studies have demonstrated that ingenol mebutate undergoes significant metabolism in human hepatocytes, with the principal routes of metabolism identified as hydrolysis and hydroxylation. The major

metabolic product was identified as a hydroxylated metabolite of PEP0XX (an unnamed metabolite of ingenol mebutate).

No population subgroup analyses have been performed for the purposes of PK or product metabolism analyses in humans. No clinical drug interaction studies have been conducted. Such studies would not be relevant, as no systemic levels of ingenol mebutate or its two isomers, PEP015 and PEP025, have been quantifiable in any clinical studies evaluating PK to date (i.e., concentrations were below the LLOQ).

No clinical studies on human pharmacodynamics have been conducted to date. Consequently, human PD data are not available and no PK/PD correlation studies have been performed nor has any PK/PD relationship been established. The mode of action of PEP005 has been established on preclinical models using cell lines and animal models.

4 OVERVIEW OF EFFICACY

Two dosing regimens being requested for marketing approval are:

- For treatment of AK lesions on head (face and scalp) locations, PEP005 Gel, 0.015%, applied topically once daily for three consecutive days,
- For treatment of AK lesions on non-head (trunk and extremities) locations, PEP005 Gel, 0.05%, applied topically once daily for two consecutive days.

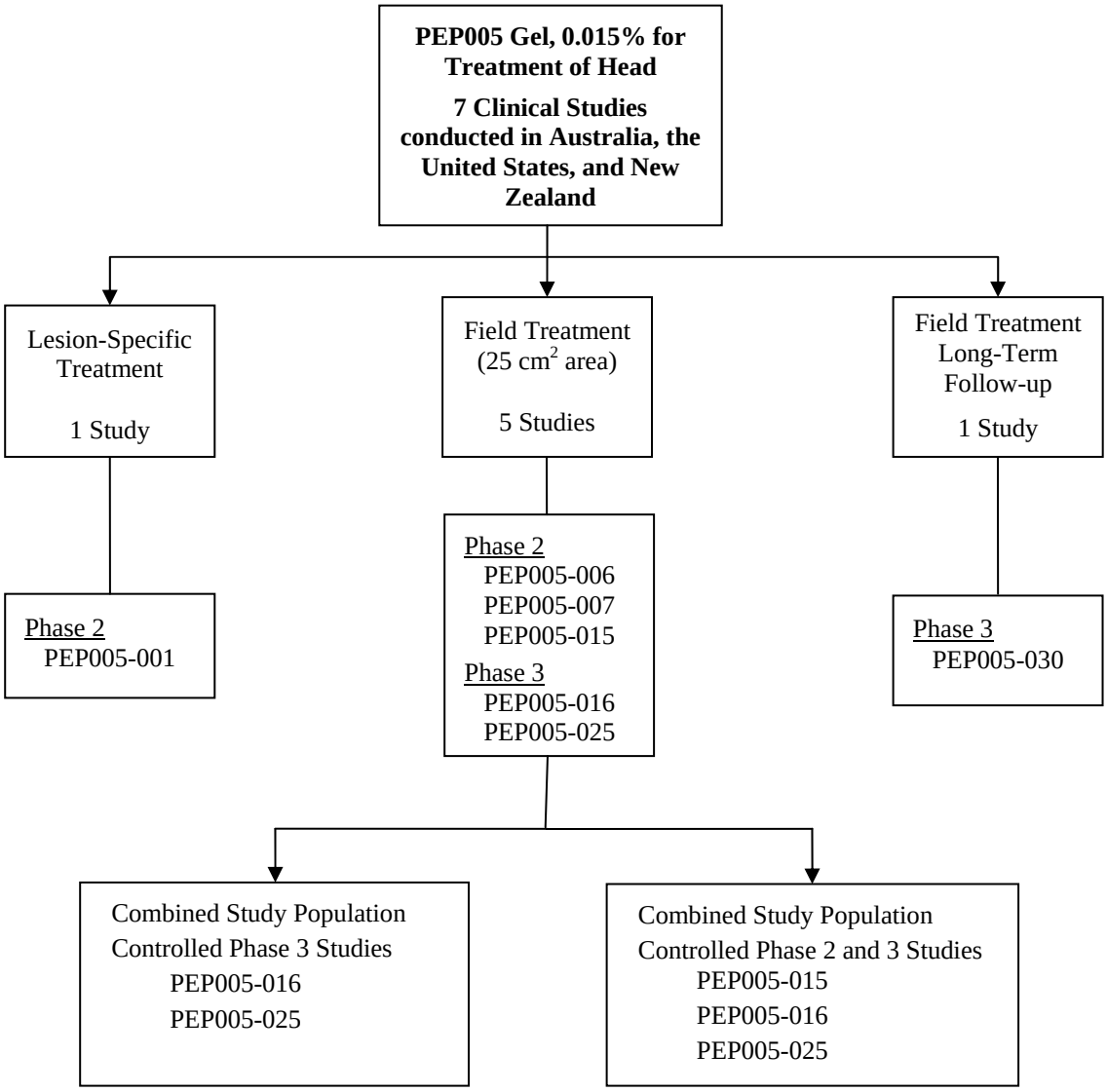
4.1 CLINICAL STUDIES EVALUATED

4.1.1 Head (Face and Scalp) Locations

For the head (face and scalp) clinical development program, there are seven studies that evaluated PEP005 Gel (Figure 2). Five studies (PEP005-016, PEP005-025, PEP005-015, PEP005-006, and PEP005-007) provide efficacy data for field treatment of PEP005 Gel to a defined 25 cm^2 skin area containing four to eight AK lesions located on the head with efficacy assessed at Day 57 (study exit); all five were included in the comparative efficacy results in Module 2.7.3. The sixth trial (PEP005-030) was a long-term follow-up study in patients who achieved complete clearance at Day 57 in studies PEP005-016 and PEP005-025. No study medication was administered during PEP005-030 and data are relevant to the persistence of efficacy. The seventh trial was a lesion-specific study (PEP005-001) which allowed up to five lesions to be treated on multiple anatomical sites (head and non-head locations) and therefore, is not discussed further in this overview.

In order to further evaluate the efficacy of PEP005 Gel, data were pooled across studies and referred to as “combined studies populations”. Two combined studies populations are presented in this overview (Figure 2). One combined studies population pooled data from PEP005-016 and PEP005-025 and another pooled data PEP005-016, PEP005-025, and PEP005-015. PEP005-016 and PEP005-025 were the adequate and well-controlled Phase 3 studies that evaluated the proposed dosage regimen of PEP005 Gel for treatment of the head locations, i.e., 0.015% applied topically for three consecutive days (Days 1, 2, and 3). PEP005-015 was a dose-ranging study that included the proposed dosage regimen treatment on head locations. These three studies were randomised, double-blind, vehicle-controlled, parallel group studies. Study medication was supplied as unit-dose tubes and patient-applied at home to a contiguous 25 cm^2 treatment area.

Figure 2: Clinical Studies Included in the Efficacy Evaluation of Head Locations



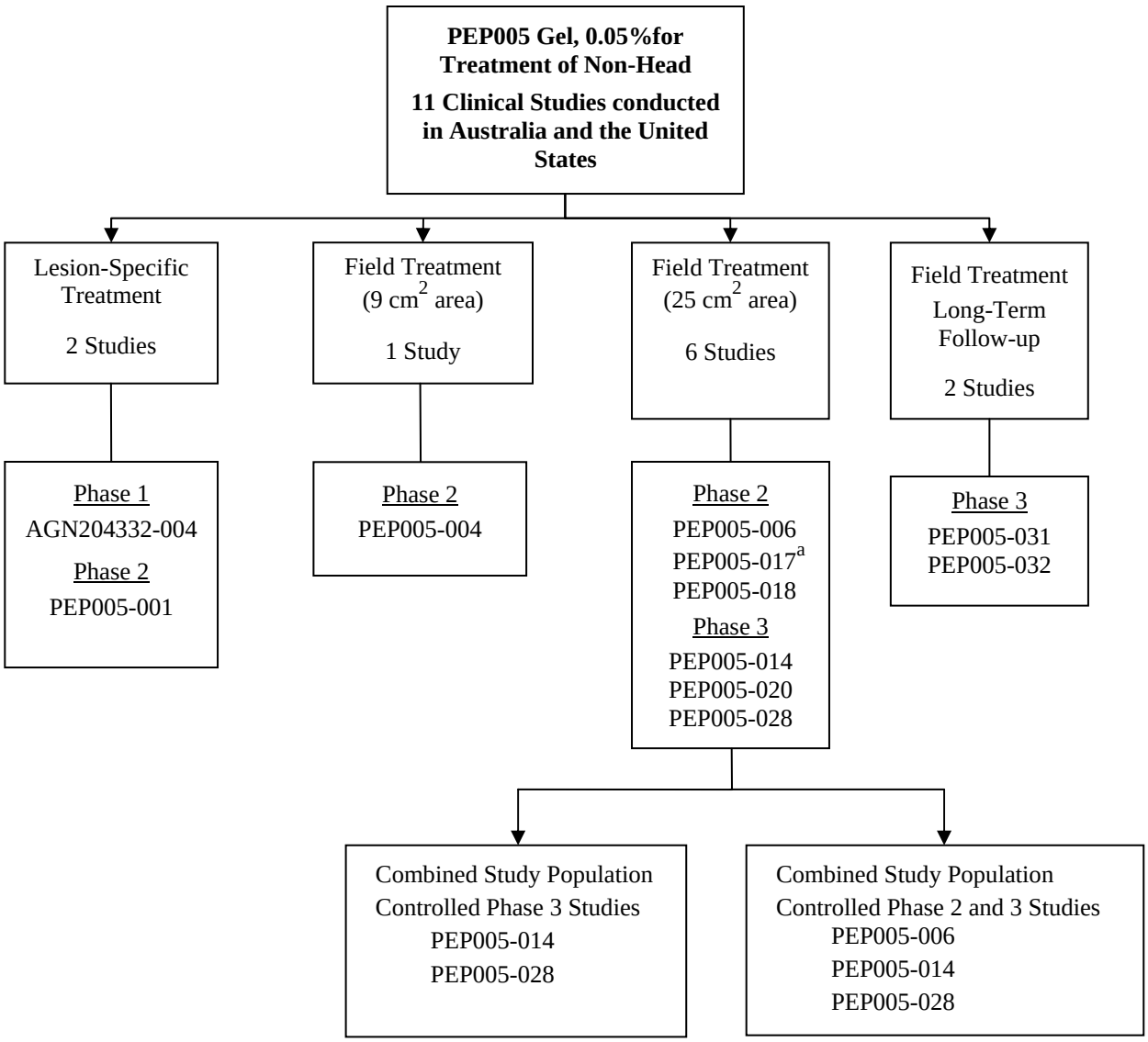
4.1.2 Non-Head (Trunk and Extremities) Locations

For the non-head (trunk and extremities) clinical development program, there are 11 studies that evaluated PEP005 Gel (Figure 3). Six studies (PEP005-014, PEP005-028, PEP005-006, PEP005-018, PEP005-020, and PEP005-017) provide efficacy data for field treatment of PEP005 Gel to a defined 25 cm^2 skin area containing four to eight AK lesions located on trunk and extremities with efficacy assessed at Day 57; all six were included in the comparative efficacy results in Module 2.7.3. Two trials (PEP005-031 and PEP005-032) were long-

term follow-up studies. PEP005-031 evaluated patients who achieved complete clearance at Day 57 in study PEP005-020 and PEP005-032 evaluated patients who achieved complete clearance at Day 57 in study PEP005-028. No study medication was administered in PEP005-031 or PEP005-032 and data are relevant to the persistence of efficacy. There was one study (PEP005-004) where PEP005 Gel was applied to a small field of treatment (9 cm^2) that included a single target lesion with efficacy endpoints assessed at Day 29. Two lesion-specific studies (AGN204332-004 and PEP005-001) were included where study medication was applied to individual AK lesions (i.e., lesion-specific therapy) rather than to a field of skin. These last three studies (PEP005-004, AGN204332-004 and PEP005-001) are therefore not discussed further in this overview.

In order to further evaluate efficacy, data were pooled across studies and referred to as "combined studies populations". In this overview, two combined studies populations are presented (Figure 3). One combined studies population pooled data from PEP005-014 and PEP005-028 and another pooled data from PEP005-014, PEP005-028, and PEP005-006. PEP005-014 and PEP005-028 were the adequate and well-controlled Phase 3 studies that evaluated the proposed dosage regimen for approval of PEP005 Gel for treatment of non-head locations, i.e., 0.05% applied topically for two consecutive days (Days 1 and 2). Unit-dose tubes were used for study medication application by the patient at home in these two studies (PEP005-014 and PEP005-28). PEP005-006 was a dose-ranging study that included the proposed dosage regimen for approval of PEP005 Gel.

Figure 3: Clinical Studies Included in the Efficacy Evaluation of Non-Head Locations



[a] For PEP005-017, an area of 100 cm^2 was treated and assessed for safety; efficacy was assessed in a 25 cm^2 area within the 100 cm^2 treatment area.

4.2 EFFICACY ENDPOINTS

The comparative efficacy analyses for head and non-head locations used the same efficacy endpoints. For the combined studies populations, the primary efficacy endpoint was complete

clearance, defined as the proportion of patients at Day 57 with no clinically visible AK lesions in the selected treatment area. For the head location, this endpoint was prespecified as the primary endpoint in the two adequate and well-controlled Phase 3 studies (PEP005-016 and PEP005-025) and the Phase 2 dose-ranging study (PEP005-015). For the non-head location, this endpoint was prespecified as the primary endpoint in the two adequate and well-controlled Phase 3 studies (PEP005-014 and PEP005-028) but was a secondary endpoint in the Phase 2 dose-ranging study (PEP005-006). The secondary endpoint was partial clearance rate, defined as the proportion of patients at Day 57 with a 75% or greater reduction in the number of clinically visible AK lesions identified at baseline in the selected treatment area. Percent reduction from baseline in the total number of AK lesions at Day 57 was an additional endpoint.

4.3 STATISTICAL ANALYSIS

For the head locations, the primary efficacy analysis in the Phase 3 studies (PEP005-016 and PEP005-025) compared complete clearance rates across treatment groups (active vs. vehicle) using the Cochran-Mantel-Haenszel (CMH) test statistic. In each of these studies, in order to obtain at least eight patients per site per treatment group, study sites yielding fewer than 16 patients were combined in order of geographical proximity, referred to as “analysis sites”. The exact composition of these “analysis sites” was determined and documented prior to breaking the study blind. The stratification for CMH analyses was based on the analysis sites, not on the actual study sites.

For the non-head locations, the primary efficacy analysis in the Phase 3 studies (PEP005-014 and PEP005-028) also compared complete clearance rates across treatment groups (active vs. vehicle) using the CMH test statistic. The CMH analysis for PEP005-014 was stratified on anatomical location and the CMH analysis for study PEP005-028 was stratified on analysis site. As part of this efficacy summary a CMH analysis for PEP005-014 stratified on analysis site is also presented.

For each Phase 3 study for the head and non-head locations, missing values were imputed using the last observation carried forward (LOCF) method. A sensitivity analysis of complete clearance assumed that all patients who missed the Day 57 visit or were outside the visit window (≤Day 50 or ≥Day 85) did not achieve complete clearance. In addition, complete clearance rates were compared across treatment groups by location of treatment area (face or scalp for head and arm, back of hand, or “other” [back, shoulder, leg or chest] for non-head). Statistical tests were two-sided with a significance level of $\alpha = 0.05$. Analyses of study

results were prespecified prior to database lock and unblinding. As part of this efficacy summary, two additional analyses of complete clearance were performed for each study. An additional sensitivity analysis was performed for complete clearance rates in which all active treatment patients who missed the Day 57 visit or were outside the visit window (≤Day 50 or ≥Day 85) were considered as not achieving complete clearance and all vehicle patients who missed the Day 57 visit or were outside the visit window were considered as achieving complete clearance. Furthermore, clearance rates were compared across treatment groups using a logistic regression model with terms for treatment, analysis site, and anatomical location.

4.4 PATIENT POPULATION

For both the head and non-head clinical development programs, the relevant features of the patient populations who participated in the Phase 3 studies included entry criteria of four to eight clinically typical, visible, and discrete AK lesions within a contiguous 25 cm^2 treatment area. Treatment area lesions were not allowed to have an atypical clinical appearance (e.g., hypertrophic, hyperkeratotic, recalcitrant disease [had cryosurgery on two previous occasions] and/or cutaneous horns). In addition, the location of the selected treatment area could not be within 5 cm of an incompletely healed wound or within 10 cm of a suspected basal cell carcinoma (BCC) or SCC. In the Phase 3 studies conducted for the head locations, patients were not allowed to have been previously treated with PEP005 Gel; only 1 patient participated who was classified as an exclusion criterion for this. In the Phase 3 studies conducted for the non-head locations, patients were not allowed to have been previously treated with PEP005 Gel in the selected treatment area; no patients participated who met this exclusion criterion. No patients participated in multiple Phase 3 studies. Evidence of skin conditions other than the study indication that would interfere with evaluation of the study medication (e.g., eczema, unstable psoriasis, xeroderma pigmentosum) were not allowed. Exclusion criteria also stipulated restrictions for prohibited treatments and procedures: (e.g., cryotherapy within 2 cm of the selected treatment area and within 2 weeks prior to screening; systemic cytotoxic agents or immunosuppressants within 4 weeks prior to screening; 5-FU, imiquimod, diclofenac or photodynamic therapy within 2 cm of the selected treatment area and within 8 weeks prior to screening).

For both head and non-head locations, most of the patients (> 90%) in the Phase 3 studies met the inclusion and exclusion criteria and are representative of the population which will use PEP005 Gel.

Of note, 66% of patients treated with PEP005 Gel in the Phase 3 studies had a Fitzpatrick skin type of I or II and 94% had a Fitzpatrick skin type of I, II, or III. These fair skin patients are not only representative of the majority of individuals who develop AK in Australia and the US, as studied in these trials, but also of Northern European individuals.(9,10,11)

Elderly and very elderly patients participated in these studies. Across the two Phase 3 studies for the head (face and scalp) location, 48% were ≥65 years and 18% were ≥75 years. Across the two Phase 3 studies for the non-head (trunk and extremities) locations, 58% were ≥65 years and 21% were ≥75 years.

A paediatric subpopulation was not included in the studies conducted with PEP005 Gel because AK does not occur in the paediatric population except in rare cases. These include a few rare genetic diseases (72), e.g., albinism (especially in near-equatorial countries in Africa) (76,77, 78), genodermatoses such as xeroderma pigmentosum (79,80,81,82) and Rothmund-Thomson syndrome.(83)

Subpopulations containing pregnant or lactating women were not included in the studies conducted with PEP005 Gel because both pregnancy and lactation were exclusion criteria in all protocols.

4.5 EFFICACY RESULTS

4.5.1 Head (Face and Scalp) Locations

Efficacy results in individual studies of interest (PEP005-016, PEP005-025, and PEP005-015) and combined studies populations for the head (face and scalp) locations are summarised in Table 1.

Table 1: Efficacy Results in Individual Studies of Interest and Combined Studies Populations, Head Locations: Intent-to-treat Population

	PEP005-016		PEP005-025		PEP005-015		Controlled Phase 3 Studies[a]		Controlled Phase 2 and 3 Studies[b]	
Efficacy Parameter	**PEP005, 0.015% (N=135)**	**Vehicle (N=134)**	**PEP005, 0.015% (N=142)**	**Vehicle (N=136)**	**PEP005, 0.015% (N=32)**	**Vehicle (N=33)**	**PEP005, 0.015% (N=277)**	**Vehicle (N=270)**	**PEP005, 0.015% (N=309)**	**Vehicle (N=303)**
Complete Clearance										
n (%)	50 (37.0)	3 (2.2)	67 (47.2)	7 (5.1)	16 (50.0)	3 (9.1)	117 (42.2)	10 (3.7)	133 (43.0)	13 (4.3)
95% Confidence Interval	28.9, 45.8	0.5, 6.4	38.8, 55.7	2.1, 10.3	31.9, 68.1	1.9, 24.3	36.4, 48.3	1.8, 6.7	37.4, 48.8	2.3, 7.2
P value	<0.001		<0.001		<0.001		<0.001			
Partial Clearance										
n (%)	81 (60.0)	9 (6.7)	96 (67.6)	11 (8.1)	23 (71.9)	4 (12.1)	177 (63.9)	20 (7.4)	200 (64.7)	24 (7.9)
95% Confidence Interval	51.2, 68.3	3.1, 12.4	59.2, 75.2	4.1, 14.0	53.3, 86.3	3.4, 28.2	57.9, 69.6	4.6, 11.2	59.1, 70.1	5.1, 11.6
P value	<0.001		<0.001		<0.001		<0.001			
Percent Reduction in AK Lesions										
n	131	133	142	136	32	33	273	269	305	302
Median	83	0	87	0	94	0	83	0	83	0
Range	-50, 100	-100, 100	-25, 100	-100, 100	0, 100	-25, 100	-50, 100	-100, 100	-50, 100	-100, 100

[a] Controlled Phase 3 studies (PEP005-016 and PEP005-025)

[b] Controlled Phase 2 and 3 studies (PEP005-015, PEP005-016, and PEP005-025); for study PEP005-015 only the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.015% three day) and the corresponding vehicle gel three day group were included.

Percent reduction = 100* (Baseline AK Lesion Count – Day 57 AK Lesion Count)/(Baseline AK Lesion Count)

For PEP005-016 and PEP005-025, P value is for comparing active treatment vs. vehicle, using the CMH test stratifying on site. For PEP005-015, P value is for comparing active treatment vs. vehicle, using Fisher's Exact test. The 95% Confidence Interval uses the exact binomial method.

For combined studies populations, P value is for comparing active treatment vs. vehicle, using a logistic regression model with treatment, study, and anatomical location.

Source: Module 5.3.5.3, Tables 3.3, 3.4, 3.5, 3.6, 3.7, and 3.12

For the head locations, the results of the two Phase 3 studies demonstrate that PEP005 Gel, 0.015% applied once daily for three consecutive days on the face/scalp was efficacious. The results of the primary efficacy analyses were statistically significant for both well-controlled studies. At Day 57, 37% and 47% of the PEP005 Gel-treated patients achieved complete clearance compared to 2% and 5% of vehicle gel-treated patients in Study PEP005-016 and PEP005-025, respectively (Study PEP005-016, $p < 0.001$; Study PEP005-025, $p < 0.001$).

Results of other efficacy analyses provided additional confirmation of the treatment effect. Findings from the secondary analysis were consistent between the studies; 60% and 68% of the PEP005 Gel-treated patients achieved partial clearance compared to 7% and 8% of vehicle gel-treated patients in Study PEP005-016 and PEP005-025, respectively (Study PEP005-016, $p < 0.001$; Study PEP005-025, $p < 0.001$). The additional efficacy endpoint of percent reduction from baseline in the number of AK lesions was also positive and consistent across the two studies (median of 83% and 87% in the PEP005 Gel groups for PEP005-016 and PEP005-025, respectively versus 0% in the vehicle gel group for each study).

The complete clearance rate for PEP005-016 was lower than the rate seen in PEP005-025. No difference was apparent between the two studies for geographic region, age, sex, race, ethnicity, anatomical location, Fitzpatrick skin type, baseline AK lesion count, history of skin cancer or prior treatment. Thus, no reason could be identified for this variation between the complete clearance rates. However, even with this variation between the two studies, the findings were consistent in that each study was statistically significant in favour of PEP005 Gel and the results were clinically meaningful. In addition, there was a high degree of replication with all three efficacy endpoints. This ability to reproduce the positive treatment benefits increases the validity of the data and demonstrates robustness.

For the combined data, 42% of PEP005 Gel patients achieved complete clearance compared with 4% of vehicle gel patients ($p < 0.001$). In addition, 64% of PEP005 Gel patients achieved partial clearance compared to 7% of vehicle gel patients ($p < 0.001$). The results of the primary efficacy analysis confirm that the protocol recommended treatment regimen of PEP005 Gel, 0.015% applied daily for three consecutive days is effective in completely clearing AK lesions on the head (face and scalp).

Patient Reported Outcomes

Patient reported outcomes included the Treatment Satisfaction Questionnaire for Medication (TSQM) and the Skindex-16 Dermatology Survey; both are validated, self-administered instruments. Refer to Module 5.3.5.1\PEP005-016 and \PEP005-025 for full results. For both

PEP005-016 and PEP005-025, statistically significant, higher mean patient global satisfaction scores, measured by the TSQM, were seen in the PEP005 Gel group compared to vehicle gel ($p < 0.001$, each study). For the Skindex-16 Dermatology Survey, a statistically significant difference was seen with PEP005 Gel-treated patients less bothered about their skin condition for each of the three domains (symptoms, emotions, and functioning) compared to vehicle gel; the positive effect was seen at Day 29 for all three domains and continued at Day 57 ($p < 0.001$ at Day 57 for each domain, each study).

4.5.2 Non-Head (Trunk and Extremities) Locations

Efficacy results in individual controlled Phase 2 and 3 studies (PEP005-014, PEP005-028, and PEP005-006) and combined populations of controlled Phase 3 and controlled Phase 2 and 3 studies for the non-head (trunk and extremities) locations are summarised in Table 2.

Table 2: Efficacy Results in Individual Studies of Interest and Combined Studies Populations, Non-Head Locations: Intent-to-treat Population

Efficacy Parameter	PEP005-014		PEP005-028		PEP005-006		Controlled Phase 3 Studies[a]		Controlled Phase 2 and 3 Studies[b]	
	PEP005, 0.05% (N=126)	Vehicle (N=129)	PEP005, 0.05% (N=100)	Vehicle (N=103)	PEP005, 0.05% (N=42)	Vehicle (N=43)	PEP005, 0.05% (N=226)	Vehicle (N=232)	PEP005, 0.05% (N=268)	Vehicle (N=275)
Complete Clearance										
n (%)	35 (27.8)	6 (4.7)	42 (42.0)	5 (4.9)	19 (45.2)	6 (14.0)	77 (34.1)	11 (4.7)	96 (35.8)	17 (6.2)
95% Confidence Interval	20.2, 36.5	1.7, 9.8	32.2, 52.3	1.6, 11.0	29.8, 61.3	5.3, 27.9	27.9, 40.6	2.4, 8.3	30.1, 41.9	3.6, 9.7
P value	<0.001		<0.001		0.002		<0.001			
Partial Clearance										
n (%)	56 (44.4)	9 (7.0)	55 (55.0)	7 (6.8)	27 (64.3)	9 (20.9)	111 (49.1)	16 (6.9)	138 (51.5)	25 (9.1)
95% Confidence Interval	35.6, 53.6	3.2, 12.8	44.7, 65.0	2.8, 13.5	48.0, 78.4	10.0, 36.0	42.4, 55.8	4.0, 11.0	45.3, 57.6	6.0, 13.1
P value	<0.001		<0.001		<0.001		<0.001			
Percent Reduction in AK Lesions										
n	120	128	100	101	41	42	220	229	261	271
Median	69	0	75	0	83	0	75	0	75	0
Range	-25, 100	-33, 100	0, 100	-33, 100	-57, 100	-20, 100	-25 – 100	-33 – 100	-57 – 100	-33 – 100

[a] Controlled Phase 3 studies (PEP005-014 and PEP005-028)

[b] Controlled Phase 2 and 3 studies (PEP005-006, PEP005-014, and PEP005-028); for study PEP005-006 only non-scalp patients in the active treatment group which evaluated the proposed dosage regimen (PEP005 Gel, 0.05% two day) and vehicle gel group were included.

Percent reduction = 100* (Baseline AK Lesion Count – Day 57 AK Lesion Count)/(Baseline AK Lesion Count)

For PEP005-014 and PEP005-028, P value is for comparing active treatment vs. vehicle, using the CMH test stratifying on site. For PEP005-006, P value is for comparing active treatment vs. vehicle, using Fisher's Exact test. The 95% Confidence Interval uses the exact binomial method.

For combined studies populations, P value is for comparing active treatment vs. vehicle, using a logistic regression model with treatment, study, and anatomical location.

Source: Module 5.3.5.3, Tables 9.1, 9.2, 9.6, 9.7, 9.8 and 9.14

For the non-head locations, the results of the two Phase 3 studies demonstrate that PEP005 Gel, 0.05% applied once daily for two consecutive days for trunk/extremities was efficacious. The results of the primary efficacy analyses were statistically significant for both well-controlled studies. At Day 57, 28% and 42% of the PEP005 Gel-treated patients achieved complete clearance compared to 5% in each of the vehicle gel groups in Study PEP005-014 and PEP005-028, respectively (Study PEP005-014, $p < 0.001$; Study PEP005-028, $p < 0.001$).

Results of other efficacy analyses provided additional confirmation of the treatment effect. Findings from the secondary analysis were consistent between the studies; 44% and 55% of the PEP005 Gel-treated patients achieved partial clearance compared to 7% in each of the vehicle gel groups in Study PEP005-014 and PEP005-028, respectively (Study PEP005-014, $p < 0.001$; Study PEP005-028, $p < 0.001$). The additional efficacy endpoint of percent reduction from baseline in the number of AK lesions was also positive and consistent across the two studies (median of 69% and 75% in the PEP005 Gel groups for PEP005-014 and PEP005-028, respectively versus 0% in the vehicle gel group for each study).

The complete clearance rate for PEP005-014 was lower than the rate seen in PEP005-028. No difference was apparent between the two studies for geographic region, age, sex, race, ethnicity, anatomical location, Fitzpatrick skin type, baseline AK lesion count, history of skin cancer or prior treatment. Thus, no reason could be identified for this variation between the complete clearance rates. However, even with this variation between the two studies, the findings were consistent in that each study was statistically significant in favour of PEP005 Gel and the results were clinically meaningful. In addition, there was a high degree of replication with all three efficacy endpoints. This ability to reproduce the positive treatment benefits increases the validity of the data and demonstrates robustness.

For the combined data, 34% of PEP005 Gel patients achieved complete clearance compared with 5% of vehicle gel patients ($p < 0.001$). In addition, 49% of PEP005 Gel patients achieved partial clearance compared to 7% of vehicle gel patients ($p < 0.001$). The results of the primary efficacy analysis confirm that the protocol recommended treatment regimen of PEP005 Gel, 0.05% applied daily for two consecutive days is effective in completely clearing AK lesions on non-head (trunk and extremities) locations.

Patient Reported Outcomes

Patient reported outcomes included the TSQM and the Skindex-16 Dermatology Survey; both are validated, self-administered instruments. Refer to Module 5.3.5.1\PEP005-014 and \PEP005-028 for full results. For both PEP005-014 and PEP005-028, statistically significant,

higher mean patient global satisfaction scores, measured by the TSQM, were seen in the PEP005 Gel group compared to vehicle gel ($p < 0.001$, each study). For the Skindex-16 Dermatology Survey, a statistically significant difference was seen with PEP005 Gel-treated patients more bothered by symptoms at Day 8 ($p < 0.001$, each study). At Day 57, all three domains (symptoms, emotions, and functioning) showed improvement compared to vehicle gel ($p < 0.001$ for each domain) in PEP005-028; no difference was observed in study PEP005-014.

4.6 SUBPOPULATION ANALYSES

4.6.1 Complete Clearance by Subpopulations of Demographic and Baseline Characteristics

For the head locations, the pre-specified univariate subgroup analyses showed five factors (anatomical location, number of baseline AK lesions, history of skin cancer, prior 5-FU use, and sex) that appeared to influence complete clearance. For the non-head locations, three factors (anatomical location, number of baseline AK lesions, and age) appeared to influence complete clearance.

For the head locations, the significant effect of sex can be explained by the partial confounding of sex with treatment location; all scalp patients were male. Univariate and multiple logistic regression analyses performed on patients treated on the face showed no statistical significance for sex. Nor is it surprising that patients with a history of skin cancer or those who have used 5-FU in the past do not respond as well. These patients most likely have extensive skin damage, representative of more severe disease.(84) For the non-head analysis, age was an inconsistent factor affecting complete clearance. It is probable that patients ≥ 65 years old, simply by a prolonged interval for sun exposure, may have more extensive AK lesions compared to patients < 65 years old. Studies conducted to investigate other therapies for AK have shown that patients with extensive keratoses are more likely to only partially respond to treatment.(85,86)

For both the head and non-head locations, results based on the number of baseline lesions suggested that patients with fewer baseline lesions were more likely to achieve complete clearance. As seen in at least one of the non-head Phase 3 studies (PEP005-028), a statistically significant treatment effect was evident in PEP005 Gel patients compared to vehicle for both subgroups of baseline lesion count (4-6 and 7-8). Yet, other studies that investigated the use of imiquimod or 5-FU suggest that keratoses which are numerous and thick may only

partially respond to treatment.(85,86) Thus, clinically, it is reasonable to conclude that fields of AK with a higher number of lesions may not achieve complete clearance as often as fields with fewer AKs.

Anatomical location was the strongest predictor of complete clearance in the subpopulation analyses for both head and non-head locations. It is well established that response is influenced by anatomical location, with scalp AKs known to be more difficult to treat.(87,88) For the head locations, patients treated on the face with PEP005 Gel had a consistent treatment effect ($p < 0.001$ in each individual study and the combined studies populations). More importantly, however, a treatment effect was also seen in scalp-treated patients. Although study PEP005-016 did not demonstrate a statistically significant improvement for scalp patients who received PEP005 Gel, study PEP005-025 and the combined populations both demonstrated statistically significant improvement for scalp patients treated with PEP005 Gel.

Reduced responsiveness to treatment of AK lesions on the extremities is also well documented in studies conducted with other treatments for AK.(89,90) For the non-head locations, a treatment effect was seen for PEP005 Gel relative to vehicle gel for each anatomical location (arm, back of hand, and “other” non-head locations). Although a statistically significant improvement was not seen in study PEP005-028 for “other” (back, shoulder, leg or chest) non-head locations (probably due to small sample size), a statistically significant improvement in complete clearance rate was seen for patients treated on “other” non-head locations in study PEP005-014 and the combined populations.

Nonetheless, for each anatomical location, the results of the combined studies population demonstrate that PEP005 Gel is effective for all head and non-head locations based on evaluating patients treated on the face, scalp, arm, back of hand, and “other” non-head (back, shoulder, leg, or chest) locations separately.

4.6.2 Exploratory Analyses of Local Skin Response with Efficacy

The assessment of safety included local skin responses (LSRs); data for LSRs are presented in Module 2.7.4 and summarised in this overview in Section 5.5.3. For treatment on both the head and non-head locations, exploratory analyses were performed to examine the association of LSRs with efficacy for patients treated with PEP005 Gel in the combined controlled Phase 3 studies and combined controlled Phase 2 and 3 studies population. The vehicle gel patients were not included. These analyses were not pre-specified.

Two types of exploratory analyses were performed, as follows:

1. The correlation of complete clearance, partial clearance, and percent reduction in AK lesion count with the maximum composite LSR score, erythema, swelling, crusting, flaking/scaling, vesiculation/pustulation, and erosion/ulceration was investigated using Spearman rank correlations.
2. For each LSR variable, the value of the maximum score which provided the greatest difference between patients who achieved complete clearance and those who did not achieve complete clearance was determined. The two subgroups defined by the value which provided the greatest difference (scores < value with greatest difference versus scores ≥ value with greatest difference) were compared in terms of the percentage of patients achieving complete clearance using Fisher's exact test for each LSR variable.

For the head locations, the combined Phase 3 studies population showed the mean maximum composite LSR scores were greater for patients with complete clearance (score of 10.1) than for patients who did not achieve complete clearance (score of 8.4). Similar findings were seen with the non-head locations; the mean maximum composite LSR scores were greater for patients with complete clearance (score of 7.5) than for patients who did not achieve complete clearance (score of 6.4).

In both the head and non-head locations, these exploratory analyses of LSR with efficacy showed there were consistent, significant positive associations of maximum composite LSR score, maximum swelling score, and maximum erythema score with complete clearance, partial clearance, and percent reduction in AK lesion count. For the head locations, patients with a maximum composite score of at least 10 had a complete clearance rate of 54% versus 35% for patients with a score less than 10. For the non-head locations, patients with a maximum composite score of at least 6 had a complete clearance rate of 41% versus 26% for patients with a score less than 6. In both the head and non-head locations, the maximum vesiculation scores showed a trend for association with complete clearance that was sometimes statistically significant. The maximum flaking and crusting scores did not seem to be associated with achieving complete clearance.

4.7 DATA ON RECURRENCE

Long-term studies were conducted to assess the recurrence rate following short-term treatment with PEP005 Gel. Patients who achieved complete clearance of AK lesions in the selected treatment area at Day 57 of the previous study were eligible and those enrolled were followed at Months 3, 6, 9, and 12 after the Day 57 visit. Recurrence was defined as any newly identified AK lesion in the selected treatment area.

4.7.1 Head (Face and Scalp) Locations

For the head locations, PEP005-030 was the long-term follow-up study in patients who achieved complete clearance at Day 57 in studies PEP005-016 and PEP005-025. Patient-based and lesion-based recurrence rates are summarised in Table 3.

Table 3: Recurrence: Head Locations

Patient-Based Recurrence[a]		**Lesion-Based Recurrence[b]**	
	PEP005, 0.015% (N=108)		**PEP005, 0.015% (N=108)**
3-month		***3-month***	
N	107	N	107
Percent	16.8	Mean (SD), %	3.8 (9.2)
95% CI	11.0, 25.4	Min, Max	0.0, 50.0
6-month		***6-month***	
N	86	N	103
Percent	33.3	Mean (SD), %	8.8 (15.2)
95% CI	25.1, 43.2	Min, Max	0.0, 80.0
9-month		***9-month***	
N	68	N	102
Percent	46.0	Mean (SD), %	9.5 (14.4)
95% CI	37.0, 56.1	Min, Max	0.0, 62.5
12-month		***12-month***	
N	55	N	100
Percent	53.9	Mean (SD), %	12.8 (19.1)
95% CI	44.6, 63.7	Min, Max	0.0, 120.0

CI = confidence interval

[a] The patient-based recurrence rate was defined as any newly identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study. Recurrence rate = the Kaplan-Meier 'failure' estimate at the target study day of the visit expressed as a percentage.

[b] The lesion-based recurrence rate for each patient with an assessment in the visit window was defined as the ratio of the number of new/recurred lesions at the visit to the number of lesions at Baseline in the previous Phase 3 study, and expressed as a percentage. For patients who received treatment for lesions in the treatment area, the number of new/recurred lesions was carried forward to visits following the administration of treatment, if no lesions were observed at these visits.

Source: Module 5.3.5.3, Table 6.3.

At 12 months of follow-up, 54% of patients who had been treated with PEP005 Gel in the previous Phase 3 studies (N=108), had at least one new or recurrent AK lesion within the selected treatment area. The estimated median time to lesion recurrence was 365 days. Based

on the number of lesions observed within the treatment area during 12 months of follow-up relative to the number of lesions at baseline (determined prior to treatment with PEP005 Gel in the Phase 3 studies), the mean lesion-based recurrence rate was 13%.

4.7.2 Non-Head (Trunk and Extremities) Locations

For the non-head locations, PEP005-031 was the long-term follow-up study in patients who achieved complete clearance at Day 57 in study PEP005-020 and PEP005-032 was the long-term follow-up study in patients who had complete clearance in study PEP005-028. Data were combined for the two long-term follow-up studies for the non-head locations. Patient-based and lesion-based recurrence rates are summarised in Table 4.

Table 4: Recurrence: Non-Head Locations

Patient-Based Recurrence[a]		**Lesion-Based Recurrence[b]**	
	PEP005, 0.05% (N=76)		**PEP005, 0.05% (N=76)**
3-month		***3-month***	
N	74	N	74
Percent	18.9	Mean (SD), %	6.7 (17.7)
95% CI	11.7, 29.8	Min, Max	0.0, 100.0
6-month		***6-month***	
N	59	N	71
Percent	39.5	Mean (SD), %	15.7 (28.0)
95% CI	29.4, 51.7	Min, Max	0.0, 140.0
9-month		***9-month***	
N	44	N	71
Percent	50.5	Mean (SD), %	16.1 (25.0)
95% CI	39.7, 62.4	Min, Max	0.0, 140.0
12-month		***12-month***	
N	36	N	71
Percent	56.0	Mean (SD), %	13.2 (23.0)
95% CI	45.1, 67.6	Min, Max	0.0, 140.0

CI = confidence interval

[a] The patient-based recurrence rate was defined as any newly identified AK lesion in the selected treatment area for patients who achieved complete clearance at Day 57 of the previous Phase 3 study. Recurrence rate = the Kaplan-Meier 'failure' estimate at the target study day of the visit expressed as a percentage.

[b] The lesion-based recurrence rate for each patient with an assessment in the visit window was defined as the ratio of the number of new/recurred lesions at the visit to the number of lesions at Baseline in the previous Phase 3 study, and expressed as a percentage. For patients who received treatment for lesions in the treatment area, the number of new/recurred lesions was carried forward to visits following the administration of treatment, if no lesions were observed at these visits.

Source: Module 5.3.5.3, Table 14.3.

At 12 months of follow-up, 56% of patients who had been treated with PEP005 Gel in the previous Phase 3 studies (N=76), had at least one new or recurrent AK lesion within the selected treatment area. The estimated median time to lesion recurrence was 274 days. Based on the number of lesions observed within the treatment area during 12 months of follow-up relative to the number of lesions at baseline (determined prior to treatment with PEP005 Gel in the Phase 3 studies), the mean lesion-based recurrence rate was 13%.

4.7.3 Summary of Recurrence Data

As discussed in Section 1.4.6, the most relevant studies with other topical products to consider for comparison with the PEP005 Gel programme are the prospective Phase 3 follow-up studies of 12–18 months duration conducted with imiquimod.(56,57,58) In one study, patients who had complete clearance 4 weeks after one or two treatment courses (3 times/week for 4 weeks) were assessed 12 months later. The patient-based recurrence rate was 39% following treatment with imiquimod 5% cream and the lesion-based recurrence was 9%.(57) In a second study, patients received imiquimod 5% cream three times a week for 16 weeks or two times a week for 16 weeks. After a median follow-up time of 16 months, the patient-based recurrence rate was 25% for the patients who received imiquimod 3 times a week (N = 77) and 43% for those who received treatment two times a week (N = 54). Lesion–based recurrence was not reported. (56) In a third study, patients received imiquimod 3.75% or 2.5% cream using two two-week or three-week cycles of daily dosing. After 12 months, for the imiquimod 3.75% cream, recurrence was 55% (N = 42) for patients who received the two-week cycles and 42% (N = 48) for patients who received the three-week cycles. For imiquimod 2.5% cream, recurrence was 67% (N = 39) for patients who received the two-week cycles and 52% (N = 37) for patients who received the three-week cycles. Lesion-based recurrence was not reported.(58)

For PEP005 Gel at 12 month follow-up, patient-based recurrence was 54% for head (face and scalp) locations and 56% for non-head (trunk and extremities) locations. Lesion-based recurrence at 12 month follow-up was 13% for each (head and non-head locations).

Limitations always exist when citing results from published literature. In addition, variability is evident as seen with the differences in patient-based recurrence rates across the 3 prospective Phase 3 imiquimod follow-up studies (recurrence ranged from 25-67%). The most recently published data on imiquimod (58), however, reports patient-based recurrence rates which are consistent with the rates seen in the PEP005 Gel studies (42-67% for imiquimod whereas recurrence for PEP005 Gel was 54-56%). Lesion-based recurrence was reported in one of the imiquimod studies (57); findings are also consistent with the PEP005 Gel studies (9% for imiquimod where as PEP005 Gel was 13%).

4.8 EFFICACY CONCLUSIONS

Data from the efficacy analyses support the following conclusions regarding field application of PEP005 Gel for the treatment of AK lesions:

- The target populations studied in the head (face and scalp) and non-head (trunk and extremities) locations are representative of the patients who will use PEP005 Gel.
- Studies were conducted in the United States, Australia, and New Zealand.
- For the head (face and scalp) locations, the protocol recommended treatment regimen of PEP005 Gel, 0.015% applied daily for three consecutive days is effective in completely clearing AK lesions. The combined Phase 3 data showed 42% of PEP005 Gel patients achieved complete clearance compared with 4% of vehicle gel patients ($p < 0.001$).
- For the non-head (trunk and extremities) locations, results confirm that the protocol recommended treatment regimen of PEP005 Gel, 0.05% applied daily for two consecutive days is effective in completely clearing AK lesions. The combined Phase 3 data showed 34% of PEP005 Gel patients achieved complete clearance compared with 5% of vehicle gel patients ($p < 0.001$).
- Results of other efficacy analyses provided additional confirmation of the treatment effect. For the head (face and scalp) locations, 64% of PEP005 Gel patients achieved partial clearance compared to 7% of vehicle gel patients ($p < 0.001$). For the non-head (trunk and extremities) locations, 49% of PEP005 Gel patients achieved partial clearance compared to 7% of vehicle gel patients ($p < 0.001$). The additional efficacy endpoint of percent reduction from baseline in the number of AK lesions was also positive and consistent for both the head and non-head studies.
- Patient-reported outcomes, as measured by the TSQM and Skindex-16 Dermatology Survey, showed positive effects for PEP005 Gel.
- Anatomical location is a strong predictor of complete clearance, as seen in the subpopulation analyses for both head and non-head locations. In two instances, a particular anatomical location within an individual study did not demonstrate a statistically significant improvement in complete clearance rate, including scalp patients in PEP005-016 and patients treated on “other” non-head locations (back, shoulder, leg, or chest) in PEP005-028. In each case, PEP005 Gel numerically favoured complete clearance in contrast to vehicle. More importantly, the results of the combined studies population demonstrate that PEP005 Gel is effective for all head and non-head locations based on evaluating patients treated on the face, scalp, arm, back of hand, and “other” non-head (back, shoulder, leg, or chest) locations separately. The individual study, however, was not powered to show statistically significant effects compared to vehicle for each anatomical location separately.

- At the 12 month follow-up, patient-based recurrence was 54% for head (face and scalp) locations and 56% for non-head (trunk and extremities) locations. Lesion-based recurrence at 12 month follow-up was 13% for each (head and non-head locations).

5 OVERVIEW OF SAFETY

5.1 SAFETY DATABASE

In total, 1774 patients/subjects received PEP005 Gel across the 25 completed studies in the clinical development programme. This safety overview focuses on the 13 studies in which patients received PEP005 Gel across a selected area of skin (i.e., field) for treatment of AK lesions. Within this group of patients, 1165 received PEP005 Gel and 632 received vehicle gel (Table 5). Data from the controlled Phase 3 studies by treatment location (i.e., face and scalp, or trunk and extremities) are also presented. Safety data from 9 additional studies, in which patients/subjects received PEP005 Gel, provide supportive information and are discussed as appropriate; these additional studies included 2 lesion-specific AK studies and 7 non-AK studies (consisting of 3 topical safety studies and 4 NMSC studies). In addition, long-term safety from 3 observational studies is presented in Section 5.3.5. As of 31 March 2011, PEP005 (ingenol mebutate) Gel is not marketed in any country; postmarketing data are therefore not available.

Table 5: Summary of Number of Patients Dosed with PEP005 Gel or Vehicle Gel for Field Treatment of AK Lesions

Population	**No. of Patients/Subjects who Received at least One Dose of Study Medication**	
	PEP005 Gel	**Vehicle Gel**
AK Lesions, Field Treatment (13 studies)	1165	632
Controlled Phase 3 Studies (PEP005-016 and PEP005-025) with PEP005 Gel, 0.015%, for Face and Scalp Locations	274	271
Controlled Phase 3 Studies (PEP005-014 and PEP005-028), with PEP005 Gel, 0.05%, for Trunk and Extremity Locations	225	232

Patients who received field treatment for AK lesions were predominantly male (79.3% PEP005 Gel vs. 75.2% vehicle), white (99.7% PEP005 Gel vs. 100.0% vehicle), and located in the United States (82.2% PEP005 Gel and 93.4% vehicle), with a mean age of approximately 66 years (range: 34 to 90 years) and a Fitzpatrick skin type of I, II, or III (93.6% PEP05 Gel vs. 94.1% vehicle). The demographics of the population were representa-

tive of patients in the general population diagnosed with AK. Epidemiology surveys have shown that the prevalence of AK increases with age, more men than women are diagnosed with AK, and patients with fair skin, specifically white skin that burns easily are at greater risk for developing AK with sun exposure.(91,92,93) One study noted that AK was rare among the black population (accounting for 0.2% of physician office visits associated with the diagnosis of AK).(93)

At baseline, patients tended to have 4 to 6 AK lesions, consistent with the protocol-specified inclusion criteria of 4 to 8 lesions for the majority of studies involving AK field treatment. The majority of patients (82.5% PEP005 Gel vs. 79.9% vehicle) reported prior cryotherapy treatment. Both imiquimod and 5-FU had been used to a lesser extent: 15% of PEP005 Gel-treated patients and 16% of placebo-treated patients had prior treatment with imiquimod; and 24.2% of PEP Gel-treated patients and 21.5% of placebo-treated patients reported prior treatment with 5-FU. Approximately half the patients had a history of skin cancer (SCC or BCC).

The vast majority of patients completed their respective study through follow-up assessments. Approximately 2% of patients in the AK field treatment studies (1.6% treated with PEP005 Gel and 2.5% treated with vehicle gel) terminated early. Reasons for termination were similar between treatment groups and included the patient's withdrawal of consent or decision to terminate (0.4% PEP005 Gel vs. 1.4% vehicle), an abnormal lab test or AE (0.3% PEP005 Gel vs. 0.5% vehicle), a protocol deviation or violation (0.3% PEP005 Gel vs. 0.3% vehicle), or the patient was lost to follow-up (0.3% PEP005 Gel vs. 0% vehicle gel). Across all AK field treatment studies, most patients had either 2 or 3 days of treatment, and 3.6% of PEP005 Gel-treated patients and 0.2% of vehicle-treated patients had only 1 day of treatment. Nearly all patients (99%) in the Phase 3 studies complied with and completed the dosing regimen.

5.2 SAFETY ANALYSIS

The safety analyses include all patients/subjects who received at least one dose of PEP005 Gel or vehicle gel. All safety data were summarised descriptively by treatment received. All adverse events (AEs) observed by the investigator or designee or reported spontaneously by the patient or in response to a direct question were noted as verbatim terms, which were subsequently mapped using a MedDRA thesaurus (version 12.0) to a system organ class (SOC) and preferred term. A treatment-related AE was a treatment-emergent AE for which the investigator assigned causality (such as "definite", "probable", or "possible") to the study medication. Each AE was graded as mild, moderate, or severe by the investigator.

Serious AEs (SAEs) were identified by the Applicant and investigator as those that resulted in death, were life-threatening, required hospitalisation or prolongation of an existing hospitalisation, resulted in persistent or significant disability or incapacity, caused a congenital anomaly or birth defect, and/or were considered medically significant. The Applicant identified and reclassified AEs as serious following review of the clinical database. Applicant-identified SAEs were all in the SOC of 'neoplasms benign, malignant and unspecified (including cysts and polyps)', with preferred terms of BCC, SCC, malignant melanoma, basosquamous carcinoma, Bowen's disease, and skin neoplasm.

Local skin responses, consisting of erythema, flaking/scaling, swelling, crusting, erosion/ulceration, and vesiculation/pustulation, were identified at each study visit by a qualified dermatologist and graded using a standardised scale of 0 to 4 to ensure consistency of data across studies. A composite LSR score was calculated by summing the scores of each of the 6 individual LSR scores, giving a maximum possible composite score of 24.

The treatment area was also assessed by a qualified dermatologist at baseline and all subsequent visits for pigmentation and scarring, both of which were graded. For the ease of summarising these data, the scores were simplified to descriptors of 'not present' or 'present' to convey the absence or presence of hypopigmentation, hyperpigmentation, or scarring at baseline and the end of the study.

In a separate evaluation, treatment-emergent AEs and LSRs (observed after the baseline visit) from the controlled Phase 3 studies PEP005-014, PEP005-016, PEP005-025, and PEP005-028 were combined by aligning each LSR term with a MedDRA preferred term as described in Table 6.

Table 6: Coding Key Used for Mapping LSR Terms to MedDRA Preferred Terms

LSR Term	MedDRA Preferred Term	Comment
Erythema	Application site erythema	-
Flaking/Scaling	Application site exfoliation	-
Crusting	Application site scab	-
Swelling	Application site swelling	-
Vesiculation/Pustulation	Application site vesicles Application site pustules	LSR Vesicles = Application site vesicle for Grade 1 responses LSR Pustulation = Application site pustules for Grade 2–4 responses
Erosion/Ulceration	Application site erosion Application site ulcer	LSR Erosion = Application site erosion for Grade 1–3 responses LSR Ulceration = Application site ulcer for Grade 4 responses
Pigmentation	Skin hyperpigmentation Skin hypopigmentation	-
Scarring	Application site scar	

5.3 SAFETY RESULTS

5.3.1 Overall Adverse Event Profile

Across all AK field treatment studies, 42.5% of PEP005 Gel-treated patients had an AE compared with 24.2% of vehicle-treated patients. The higher incidence of AEs in the PEP005 Gel-treated group is attributed to a higher rate of application site reactions occurring in patients treated with active rather than vehicle gel. The SOC of general disorders and administration site conditions had the highest incidence of AEs for patients treated with PEP005 Gel (22.7% vs. 2.8% for patients treated with vehicle). Within this SOC, application site pruritus, application site pain, and application site irritation were the most frequently reported AEs and were predominantly reported for patients treated with PEP005 Gel rather than patients treated with vehicle.

For PEP005 Gel-treated patients, AEs were more likely considered by the investigator as related to treatment compared with those for vehicle-treated patients (also attributed to the higher rate of application site reactions in the PEP005 Gel-treated patients). For PEP005 Gel-treated patients, the most frequently reported AEs considered related to study medication included application site pruritus (10.7%), application site pain (7.8%), and application site irritation (7.0%). Differences were noted with respect to the incidence of treatment-related AEs between treatment locations. In the controlled Phase 3 studies, patients treated with PEP005 Gel on the face or scalp had a higher incidence of application site pain than patients treated on the trunk or extremities (13.9% vs. 1.8%, respectively). Similarly, patients treated

on the face or scalp had eye-associated disorders, such as eyelid oedema (1.1%) and periorbital oedema (2.6%), whereas patients treated on the trunk or extremities had no reports of these events.

The majority of patients had an AE with maximum severity of mild or moderate intensity. Severe AEs were reported by 3.2% of PEP005 Gel-treated patients and 1.6% of vehicle-treated patients. Severe events occurred at a higher frequency for patients treated with PEP005 Gel compared to vehicle in the SOC of general disorders and administrative site conditions, with application site reactions (e.g., irritation, pain and pruritus) attributed for this difference between treatment groups

The emergence of an AE resulted in discontinuation of treatment for 3.2% and 0% of PEP005 Gel- and vehicle-treated patients, respectively, and discontinuation from the study for 0.1% and 0.3%, respectively (Section 5.3.3). There was one reported death in a patient who had been treated with PEP005 Gel; the death was attributed to coronary artery atherosclerosis and hypertension, considered unrelated to study medication (Section 5.3.2). Other SAEs were reported for 4.2% of PEP005 Gel-treated patients and 3.6% of vehicle-treated patients; 3 SAEs (all occurring in PEP005 Gel-treated patients and all SCC-type lesions) were considered related to study medication. An overview of AEs for the 13 AK field treatment studies is provided in Table 7.

Table 7: Overview of Adverse Events

	Controlled Phase 3 Studies				All AK Studies	
	Face and Scalp		Trunk and Extremities		All Locations	
	0.015% PEP005 Gel (N=274)	Vehicle (N=271)	0.05% PEP005 Gel (N=225)	Vehicle (N=232)	PEP005 Gel (N=1165)	Vehicle (N=632)
Patients with one or more AEs	102 (37.2%)	60 (22.1%)	75 (33.3%)	63 (27.2%)	495 (42.5%)	153 (24.2%)
Patients with one or more treatment-related AEs	72 (26.3%)	11 (4.1%)	29 (12.9%)	2 (0.9%)	312 (26.8%)	22 (3.5%)
Patients with one or more severe AEs	8 (2.9%)	4 (1.5%)	5 (2.2%)	4 (1.7%)	37 (3.2%)	10 (1.6%)
Patients with one or more severe treatment-related AEs	4 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (1.5%)	0 (0.0%)
Patients with one or more AEs leading to discontinuation of study drug	3 (1.1%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	37 (3.2%)	0 (0.0%)
Patients with one or more AEs leading to discontinuation from the study	1 (0.4%)	1 (0.4%)	0 (0.0%)	1 (0.4%)	1 (0.1%)	2 (0.3%)
Patients with one or more SAEs	6 (2.2%)	5 (1.8%)	8 (3.6%)	12 (5.2%)	49 (4.2%)	23 (3.6%)

5.3.2 Serious Adverse Events

Among the patients who received field applications of PEP005 Gel or vehicle for treatment of AK lesions, SAEs were identified (by both the investigator and Applicant [see Section 5.2]) for 4.2% of patients in the PEP005 Gel group and 3.6% of patients in the vehicle group. Of these SAEs, BCC (occurring in 1.5% of PEP005 Gel-treated patients and 1.1% of vehicle-treated patients) and SCC (0.9% of PEP005 Gel-treated patients and 0.8% of vehicle-treated patients) were the most frequently reported for both treatment groups (reflecting both investigator- and Applicant-identified events; all serious events of BCC and approximately half of the reported SCCs were reclassified as SAEs by the Applicant). Three patients (all treated with PEP005 Gel, 0.05%) had an SAE that was assessed as treatment-related; 1 patient had Bowen's disease, graded as mild and 2 patients had SCC, 1 graded as mild and the other graded as moderate. For all 3 patients, the SAE resolved following excision.

An examination of the location of occurrence of SCCs relative to the treatment area (i.e., inside vs. outside) showed that a similar proportion of patients in each treatment group (0.3% PEP005 Gel vs. 0.3% vehicle) had an SCC inside the treatment area. During long-term (12 months), observational, follow-up studies, in which efficacy and safety were assessed within the treatment area, no SCCs were reported (Section 5.3.5).

Across the 9 other studies in which patients/subjects received study drug (i.e., for lesion-specific AK treatment, for assessment of topical safety in healthy volunteers, and for treatment of NMSC), a total of 15 PEP005 Gel-treated patients and 4 vehicle-treated patients had an SAE. Patients in the NMSC studies had the highest rate of SAEs (which most frequently involved neoplasms) compared to subjects in the topical safety studies (with no SAEs) or patients in the studies that evaluated lesion-specific AK treatment. The most frequently reported SAE across the other 9 studies was BCC, which occurred in 8 (0.7%) PEP005 Gel-treated patients and 3 (0.5%) vehicle-treated patients. All serious events of BCC were classified as SAEs by the Applicant. While the majority of SAEs in these other 9 studies were considered unrelated to study medication, 2 patients had an SAE considered related: mild 'neoplasm progression', and moderate BCC, both excised.

Across all studies, there was one death, which occurred in a patient who received PEP005 Gel, 0.005% in study PEP005-015. The patient, a 58-year-old white male, died of coronary artery atherosclerosis and hypertension approximately 4 months after receiving study treatment. The investigator judged the death as not related to study medication.

5.3.3 Adverse Events Leading to Discontinuation

5.3.3.1 Discontinuation from the Study

In the 13 studies that evaluated field treatment of PEP005 Gel for AK lesions, a total of 3 patients (1 treated with PEP005 Gel and 2 treated with vehicle) discontinued from the study due to one or more AEs. The patient treated with PEP005 Gel discontinued study PEP005-016 due to severe application site (face) pain, severe eye pain, and severe periorbital oedema. The vehicle-treated patients discontinued due to multiple trauma and loss of consciousness after falling off a ladder (1 patient) and severe myocardial infarction (MI; 1 patient).

Across the 9 additional studies (lesion-specific and non-AK), 1 patient (who received PEP005 Gel, 0.05% in study PEP005-008) discontinued from the study due to diarrhoea, which was moderate in intensity.

5.3.3.2 Discontinuation of Treatment

In the 13 AK field treatment studies, a total of 37 patients (37 treated with PEP005 Gel and 0 treated with vehicle) discontinued study medication due to one or more AEs. Although patients discontinued study medication, most remained in the study for observation of AK lesion disposition and safety assessments through Day 57. Discontinuation of study medication was primarily attributed to application site reactions, notably application site irritation and application site pain, reported by 16 patients each.

Across the 9 additional studies, 4 patients discontinued dosing due to application site pain, erythema and skin exfoliation, lymphangitis, and pregnancy.

5.3.4 Analysis of Selected Groupings of Adverse Events

Adverse events within the MedDRA SOCs of infections and infestations, neoplasms, eye disorders (as well as the AE of periorbital oedema, not part of the eye disorder SOC), and cardiac disorders were examined; these AEs were selected prospectively by the Applicant because they were considered relevant to the drug, the method of delivery, and/or drug development considerations. Analyses of these selected MedDRA SOCs were performed for patients who received field application of PEP005 Gel (or placebo) for treatment of AK lesions (consisting of 1165 PEP005 Gel-treated patients and 632 placebo-treated patients [Table 5]).

Infections and infestations, as identified by the investigators, occurred in 7.6% vs. 5.5% of patients treated with PEP005 Gel vs. vehicle, respectively. Among the PEP005 Gel-treated

patients, the more commonly reported (‡ 0.5%) infections included nasopharyngitis, application site infection, upper respiratory tract infection, influenza, and urinary tract infection. In comparison, the more commonly reported infections for vehicle-treated patients were upper respiratory tract infection, bronchitis, sinusitis, gastroenteritis, nasopharyngitis, and urinary tract infection. Treatment-related infections occurred in 1.5% of PEP005 Gel treated patients and most frequently included application site infection (0.9% PEP005 Gel vs. 0.1% vehicle). The majority of infections were graded as either mild or moderate; severe events occurred in 0.3% vs. 0% of patients treated with PEP005 Gel vs. vehicle.

Neoplasms (arising at any location, i.e., outside or inside the treatment area) were reported for a similar proportion of patients treated with PEP005 Gel and vehicle (3.0% vs. 2.7%, respectively). The majority of neoplasms were graded as mild or moderate. Basal cell carcinoma and SCC were the more frequently reported types of neoplasms and occurred with similar frequency between groups (BCC: 1.5% vs. 1.1% for PEP005 Gel vs. vehicle; SCC: 0.9% vs. 0.8% for PEP005 Gel vs. vehicle). As noted in Section 5.3.2, 0.3% of patients in both treatment groups had an SCC inside the treatment area.

Examination of eye disorders included the MedDRA SOC of eye disorders as well as the preferred term of periorbital oedema within the SOC of skin and subcutaneous tissue disorders. Eye disorders and periorbital oedema occurred more frequently in the PEP005 Gel treatment group than the vehicle group; 2.3% of patients treated with PEP005 Gel and 0.3% of patients treated with vehicle had an AE within the MedDRA SOC of eye disorder, and 1.0% vs. 0% of patients in the PEP005 Gel vs. vehicle groups had periorbital oedema. By preferred term, periorbital oedema and eyelid oedema were the most frequently reported eye-associated events, which were primarily graded as mild or moderate and considered related to study treatment. There were 5 severe related events (all in patients treated with PEP005 Gel), which included periorbital oedema, eyelid oedema, eye oedema, eye pain, and eyelid ptosis. One patient had eye-associated AEs (severe eye pain and severe periorbital oedema) that resulted from inadvertent eye exposure following application of PEP005 Gel to the face; the events were considered related to study medication and the patient discontinued from the study (as noted in Section 5.3.3.1).

Cardiac disorders occurred with similar frequency between patients treated with PEP005 Gel (1.7%) and patients treated with vehicle (2.8%). The most frequently reported cardiac disorders were angina pectoris, first degree atrioventricular (AV) block, MI, and ventricular extrasystoles. Cardiac disorders were generally mild or moderate; severe events were

experienced by 0.3% of PEP005 Gel-treated patients and 0.6% of vehicle-treated patients. Treatment-related cardiac disorders were experienced by 0.2% of PEP005 Gel-treated patients (which included ventricular extrasystoles and palpitations) and 0.3% of vehicle-treated patients (which included ventricular extrasystoles, left bundle branch block (LBBB), and extrasystoles). No patient had a severe treatment-related cardiac event. One patient, treated with vehicle, discontinued from the study due to a severe, unrelated MI (as noted in Section 5.3.3.1).

5.3.5 Long-term Safety

Long-term safety was assessed in 3 prospective, longitudinal, observational studies (PEP005-030, PEP005-031, and PEP005-032) that were designed to evaluate lesion recurrence and safety within the selected treatment area over a 12-month follow-up period in patients who had achieved complete clearance of AK lesions in studies PEP005-016, PEP005-020, PEP005-025, and PEP005-028. Originally the follow-up studies included patients who had completed the Day 57 visit of the study in which they had received PEP005 Gel or vehicle; this criterion was subsequently amended to limit eligibility to patients who demonstrated complete clearance of AK lesions at the Day 57 visit. Patients who no longer met the eligibility criterion were withdrawn from the study.

A total of 198 patients had demonstrated complete clearance of AK lesions (following treatment with PEP005 Gel [184 patients] or vehicle [14 patients]) at the Day 57 visit of the prior study and were enrolled in the long-term, follow-up studies. These patients had a mean age that ranged from approximately 61 to 68 years, and the majority were male and white, with Fitzpatrick skin types of I, II, or III. During follow-up, no patient received PEP005 Gel, and 14 patients prematurely discontinued due to: withdrawal of consent (9 patients), protocol violation (2 patients), lost to follow-up (1 patient), investigator decision (1 patient), and inability to return to the study site for the 12-month visit (1 patient).

Over 12 months of follow-up, 3 of the 198 patients had an AE within the selected treatment area that consisted of a mild sun burn, a moderate haematoma, and a mild rash. All 3 AEs occurred approximately 8 to 9 months after the start of follow-up; all events resolved within 2 weeks of onset, and all were considered not related to the study drug received during the prior study.

Of the patients withdrawn from the follow-up studies due to the change in eligibility criteria, one patient had an AE of BCC within the treatment area, which was reported on Day 100 of study PEP005-031. The patient had received PEP005 Gel, 0.05%, on the back of the hand in

study PEP005-020. The BCC was graded as moderate and considered by the investigator as not related to study medication. No action was taken, and at the time of last contact, there was little or no change in the BCC. This event was reclassified as an SAE by the Applicant following review of AEs in the clinical database.

5.3.6 Combined Adverse Events and Local Skin Responses

In order to provide a comprehensive summary of safety following topical administration of PEP005 Gel, AE and LSR data (Section 5.5.3) were combined by aligning LSR terminology with MedDRA preferred terms. The combined events were evaluated for a causal relationship to PEP005 Gel in order to qualify them as adverse reactions, which were selected based on the following criteria:

- Consistently higher incidence in the PEP005 Gel group compared to the vehicle group
- For events with an incidence < 10%:
  - If the incidence in the vehicle group was > 0, the incidence in the PEP005 Gel group was at least 1% higher compared to the vehicle group; or
  - The incidence was at least 0.5% in the combined PEP005 Gel group
- For events with an incidence > 10%:
  - The incidence was at least 5% higher in the PEP005 Gel group compared to the vehicle group
- Consistency with clinical findings
- Consistency with pre-clinical findings
- Other reason for causality (such as consistent trend in the treated anatomic region)
- Medical judgment

Based on these criteria, adverse reactions are presented in Table 8, along with the frequency descriptor according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100).

Table 8: Adverse Reactions by MedDRA System Organ Class and Preferred Term (based on the Combination of Adverse Events and Local Skin Responses)

System Organ Class	Frequency
Infections and Infestations	
Application site pustules	Very common
Application site infection	Common
Nervous system disorders	
Headache	Common
Eye Disorders	
Periorbital oedema	Common
Eye lid oedema	Uncommon
General disorders and administration site conditions	
Application site erosion Application site vesicles Application site swelling Application site exfoliation Application site scab Application site erythema	Very common
Application site pain Application site pruritus Application site irritation	Common
Application site paraesthesia Application site ulcer	Uncommon

5.4 CLINICAL LABORATORY EVALUATIONS

The vast majority of clinical laboratory parameters (hematology and serum chemistry) were within normal limits at the time points measured in the studies. The proportion of patients with normal laboratory values at baseline followed by shifts away from this normal range at later time points was generally similar between treatment groups, with no apparent trend. There were no meaningful shifts or trends in any of the clinical laboratory parameters.

5.5 VITAL SIGNS AND OTHER OBSERVATIONS RELATED TO SAFETY

5.5.1 Vital Signs

Overall, throughout the development program, the vast majority of patients had vital sign values (systolic and diastolic blood pressure and heart rate) that were normal at baseline and remained normal during the study period. For AK patients who received field application of

study medication, shifts from normal values to those considered clinically significant occurred in 9–15% of patients, which was generally similar between patients treated with PEP005 Gel and those treated with vehicle. Hypertension was reported as an AE for 12 (1.0%) of the AK patients who received field applications of PEP005 Gel and for 3 (0.5%) of the AK patients who received vehicle (an additional vehicle-treated patient had an AE of increased blood pressure). One patient treated with PEP005 Gel in study PEP005-022 had moderate hypertension that was reported as an SAE; this event was considered not related to study medication. Vital signs in the other 9 studies (lesion-specific and non-AK) showed similar results, with the majority of values remaining normal throughout the studies. Overall, no clinically meaningful differences were observed between the treatment groups with respect to vital signs.

5.5.2 Electrocardiogram Results

ECGs were performed at screening and the day after the last dose of study drug in studies PEP005-014, PEP005-028, PEP005-016, and PEP005-025. ECG intervals were determined, which included PR, QRS, QT and QTc, using both the Bazett [QTcB] and Fridericia [QTcF] correction formulae. For each ECG interval in all 4 studies, mean values at pre- and postdose, and mean changes from baseline were similar between patients treated with PEP005 Gel and those treated with vehicle. All postdose ECG intervals showed minimal changes from predose values; and the direction and magnitude of the changes were generally similar between treatment groups with no apparent trend.

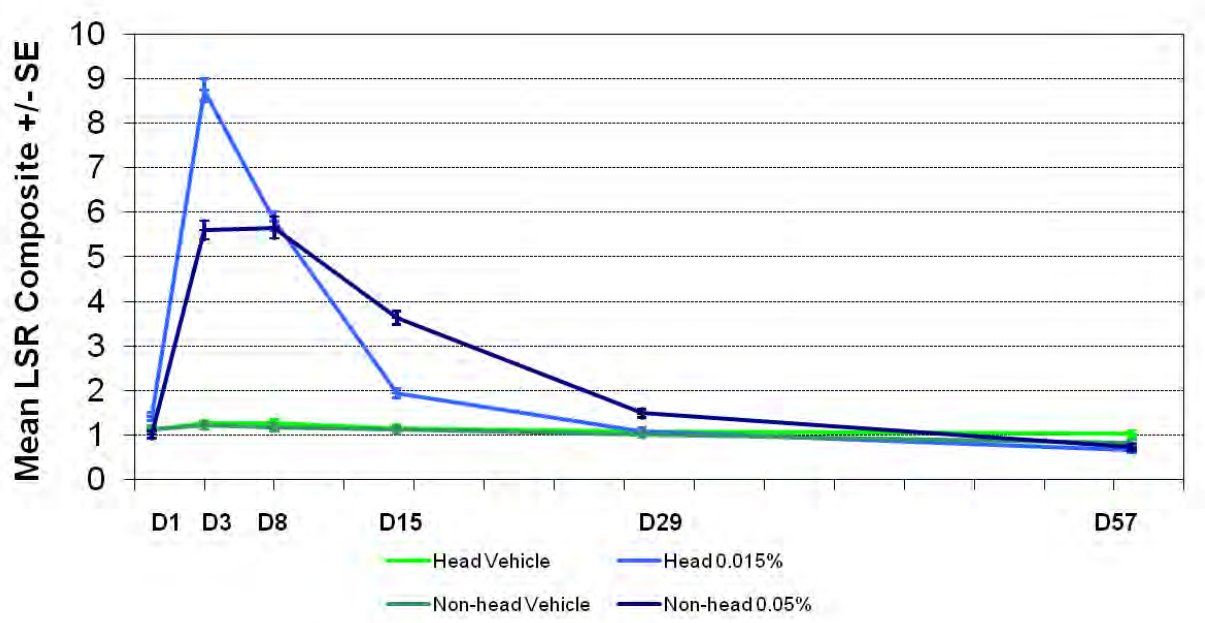
Across the 4 studies, a total of 29 patients (13 treated with PEP005 Gel and 16 treated with vehicle) had an ECG abnormality that was reported as an AE; of these, 4 patients (2 treated with PEP005 Gel and 2 treated with vehicle) had an event considered related to study medication. In the 2 PEP005 Gel-treated patients, these AEs included mild ventricular extrasystoles and mild QT prolongation. In the 2 vehicle-treated patients, the AEs included mild LBBB, mild ventricular extrasystoles, and mild QT prolongation.

ECG safety analyses (including a central tendency analysis, an outlier analysis, and a morphological analysis) were performed using data from all enrolled patients who had at least one available pre-treatment ECG and at least one post-treatment ECG in studies PEP005-014, PEP005-028, PEP005-016, and PEP005-025. The results showed that patients treated with PEP005 Gel had no clinically relevant signal of any changes in heart rate, AV conduction, cardiac depolarisation, or cardiac wave form morphology or new rhythms. The data from the central tendency and outlier analyses demonstrated no clear signal of any effect on cardiac repolarisation (a report describing these analyses is provided in Module 5, Section 5.3.5.3).

5.5.3 Local Skin Response

Following application of study medication, most PEP005 Gel-treated patients showed an increase in LSR scores relative to baseline, whereas most patients treated with vehicle showed no change from baseline LSR score; approximately 95% of AK patients who received field applications of PEP005 Gel vs. 36% of vehicle-treated patients had a post-treatment increase in LSR score. Figure 4 shows the mean composite LSR score on each observation day for patients treated on the face/scalp or trunk/extremities with PEP005 Gel or vehicle in the controlled Phase 3 studies. During the conduct of these studies, patients were instructed to contact the investigator if they had questions or concerns about an LSR or a worsening LSR; although patients in these Phase 3 studies were not observed daily, the occurrence of the peak LSR was consistent with earlier studies (e.g., PEP005-006, PEP005-007), in which patients returned to the clinic for LSR assessments daily during the dosing period.

Figure 4: Mean Composite LSR Score on Each Observation Day



Source: Module 2.7.4, Figure 2

For patients treated on the face or scalp with PEP005 Gel, 0.015% for 3 consecutive days in the controlled Phase 3 studies, the mean (– SD) maximum composite LSR score was 9.1 (– 4.1); in comparison, vehicle-treated patients had a score of 1.8 (– 1.6). The majority of

patients treated with PEP005 Gel, 0.015% had a maximum LSR score on Day 4, which returned to baseline or below by Day 15.

For patients treated on the trunk or extremities with PEP005 Gel, 0.05% for 2 consecutive days in the controlled Phase 3 studies, the mean (– SD) maximum composite LSR score was 6.8 (– 3.5); and vehicle-treated patients had a score of 1.6 (– 1.5). The majority of patients treated with PEP005 Gel had a maximum score on Days 3 or 8, which returned to baseline or below by Day 29.

For both treatment locations (face/scalp and trunk/extremities), erythema and flaking/scaling were the most common LSRs, followed by crusting and swelling. Erythema and flaking/scaling were present to some extent prior to application of study medication (reflecting presence of localised irritation at the lesion site); and these persisted with vehicle treatment and worsened following PEP005 Gel treatment. Local reactions assigned a maximum score of '4' (i.e., extending beyond the treatment area) were observed more frequently for erythema than the other LSRs, independent of treatment location (Table 9).

Table 9: Summary of Patients with a Maximum Post-baseline Local Skin Response Score in the Controlled Phase 3 Studies by Treatment Location

Local Skin Response	**Maximum Grade of 4 Post Baseline defined as follows**	**Controlled Phase 3 Studies**			
		Face/Scalp		**Trunk/Extremities**	
		0.015% PEP005 Gel (N=274)	**Vehicle (N=271)**	**0.05% PEP005 Gel (N=225)**	**Vehicle (N=232)**
Erythema	Red extending outside treatment area	66 (24.1%)	0 (0.0%)	34 (15.1%)	0 (0.0%)
Flaking / Scaling	Scaling extending outside treatment area	25 (9.1%)	0 (0.0%)	18 (8.0%)	0 (0.0%)
Crusting	Crusting extending outside treatment area	16 (5.8%)	0 (0.0%)	8 (3.6%)	0 (0.0%)
Swelling	Marked swelling extending outside treatment area	14 (5.1%)	0 (0.0%)	7 (3.1%)	0 (0.0%)
Vesiculation / Pustulation	Transudate or pustules, with or without vesicles extending outside treatment area	15 (5.5%)	0 (0.0%)	3 (1.3%)	0 (0.0%)
Erosion / Ulceration	Black eschar or ulceration	1 (0.4%)	0 (0.0%)	2 (0.9%)	0 (0.0%)

Source: Module 2.7.4, Table 44

5.5.4 Pigmentation and Scarring

The majority of patients who received field application of PEP005 Gel or vehicle for the treatment of AK lesions showed no hypopigmentation, hyperpigmentation, or scarring at baseline or the end-of-study assessments. Generally, baseline observations remained unchanged at the end of the study. Shifts that occurred for these parameters (especially for pigmentation) indicated an improvement, with 8.0% and 7.8% of PEP005 Gel-treated patients having hypo- or hyperpigmentation (respectively) at baseline that was absent at the end of the study. Vehicle-treated patients showed a similar trend: 3.5% and 4.4% had hypo- or hyperpigmentation (respectively) at baseline that was absent at the end of the study. A small percentage of patients had no observation at baseline but showed hypopigmentation (2.2% PEP005 Gel vs. 0.5% vehicle), hyperpigmentation (1.5% PEP005 Gel vs. 0.9% vehicle) or scarring (0.2% in each of the PEP005 Gel and vehicle groups) at the end of the study.

5.5.5 Abnormal Proliferation

An abnormal proliferation within the treatment area was recorded for a total of 18 patients in both the AK studies (10 patients treated with PEP005 Gel and 4 treated with vehicle) and the NMSC studies (4 patients treated with PEP005 Gel). As clinically warranted based on the findings of the examination, lesions were biopsied or excised per standard of care. Among the 10 patients with an abnormal proliferation treated with PEP005 Gel in the AK studies, biopsy results showed SCC or Bowen's disease for 4 patients (no other neoplasm was apparent in the remaining 6 patients). Among the 4 vehicle-treated patients in the AK studies, 2 patients had a neoplasm (BCC and basosquamous carcinoma). Finally, of the 4 patients with an abnormal proliferation in the NMSC studies, 2 patients with BCC at study entry had 'neoplasm progression'. Results of the abnormal proliferation findings were reported as AEs or SAEs, as appropriate.

5.5.6 Topical Safety

Results of 3 topical safety studies in healthy volunteers showed that PEP005 Gel did not produce a sensitisation response (study PEP005-005), phototoxicity (study PEP005-023), or photosensitisation (study PEP005-024).

5.5.7 Effect of Multiple Treatments of PEP005 Gel

Forty-nine patients received PEP005 Gel for field treatment of AK lesions after previously receiving PEP005 Gel in an AK or non-AK study (29 received treatment on the face or scalp and 20 on the trunk or extremities). Of the 49 patients, only 2 received treatment that possibly

overlapped in the selected treatment area. No patient participated in multiple Phase 3 studies. The median cumulative dosing duration for these 49 patients was 4 days (range 2–7 days), and the mean – SD PEP005 Gel concentration per dosing day was 0.029% – 0.016%. An assessment of AEs showed that these patients were not at higher risk for an AE or application site disorder with multiple treatments of PEP005 Gel. For the assessment of LSRs, there were too few patients for meaningful interpretation; results of the evaluation of multiple treatments of PEP005 Gel on maximum LSR composite scores are presented in Module 2.7.4, Section 4.3.1.2.

5.5.8 Patient Instructions for Application of PEP005 Gel

Early-phase clinical trials, assessing PEP005 Gel for AK, required that study medication be applied by the investigator at the study site. As clinical development of this compound progressed, later studies stipulated that the gel be applied by the patient at home. Patients were instructed to protect the finger used to apply the study medication with a glove or finger cot. Patients were also provided with instructions for handling accidental or inadvertent exposure (e.g., healthy skin, eyes, inhalation, or ingestion) to the gel.

Although no data or information from previous studies suggested protection was warranted, patient instructions for the use of gloves or finger cots were incorporated into the clinical protocols because the Applicant considered it was the most cautious and prudent approach for conducting the trials. With the conclusion of the Phase 3 program, there was no safety information to suggest that gloves/finger cots were required for application of PEP005 Gel.

Pharmacokinetic data show that there is no systemic absorption of the active ingredient and topical safety studies show no potential for skin sensitisation, photoirritation or photoallergy. PEP005 Gel is an alcohol based gel and there are no inactive ingredients that result in acute toxicity to the skin. Given these factors, the Applicant believes that patients can safely apply this product without the use of a protective finger cot and that hand washing alone is sufficient to remove any residual gel following application.

As of the time of this submission, a safety study designed to evaluate the local tolerability on the finger after exposure to PEP005 Gel followed by hand washing is ongoing. This study is an open-label, 2-arm, non-controlled trial of PEP005 Gel. Approximately 100 subjects will be randomised to either PEP005 Gel 0.05% applied topically once daily for 2 consecutive days or PEP005 Gel 0.015% applied topically once daily for 3 consecutive days. Local skin responses at and around the dominant index finger (application finger) will be assessed at

baseline and each subsequent visit using the LSR grading scale (i.e., the same scale used to conduct previous AK clinical trials).

The Applicant intends to provide safety data from this study during the review to support application instructions in the labeling.

5.5.9 Use in Pregnancy and Lactation

There are no data from the use of ingenol mebutate in pregnant or lactating women. Pre-clinical developmental toxicity studies in rats and rabbits did not demonstrate any significant reproductive toxicity potential following intravenous (IV) administration. Minor foetal abnormalities or variants were observed in the foetuses of treated rabbits; however, the findings did not suggest a clear association with IV ingenol mebutate administration and may have been incidental. Based on these studies, ingenol mebutate is not considered to be a reproductive toxicant. Risks to humans receiving topical treatment with PEP005 Gel are considered unlikely as ingenol mebutate is not absorbed systemically. As a precautionary measure, it is preferable to avoid the use of PEP005 Gel during pregnancy. During lactation, the nursing mother should be instructed that the newborn/infant avoid physical contact with the PEP005 Gel-treated area for a period of 6 hours after application.

5.6 IMPACT OF INTRINSIC AND EXTRINSIC FACTORS

Analyses were performed to evaluate a relationship between demographic and baseline characteristics and development of application site pain or application site pruritus (the only 2 AEs in the controlled Phase 3 studies that had a difference in incidence rates between the PEP005 Gel group and the vehicle group of at least 5%) or the change from baseline in mean maximum LSR composite score. For these analyses, the following demographic and baseline characteristics were considered: geographic location, age category, sex, race, Fitzpatrick skin type, treatment location, histories of cardiovascular disorders, endocrine disorders, allergy/immunologic disorders, gastrointestinal disorders, concentration of PEP005 Gel, dosing regimen (i.e., number of dosing days), prior cryotherapy, or prior therapy with either imiquimod or 5-FU.

The results of these analyses showed that patients treated on the face/scalp with the 0.015% PEP005 Gel for 3 consecutive days had a higher incidence of application site pain than patients treated on the trunk/extremities with the 0.05% PEP005 Gel for 2 consecutive days. There was no relationship observed for application site pruritus. Analysis of the change in mean maximum LSR composite score (indicative of intensity of specific local skin responses)

also showed that patients dosed with the 0.015% PEP005 Gel for 3 days on the face/scalp had a significantly greater change in the mean maximum LSR composite score (indicating greater intensity) than patients dosed with 0.05% PEP005 Gel for 2 days on trunk/extremity locations.

5.7 SAFETY CONCLUSIONS

Data from the safety database support the following conclusions regarding field application of PEP005 Gel for the treatment of AK lesions:

- Localised application site disorders (pruritus, pain, irritation) were the most commonly reported treatment-emergent AE following administration of PEP005 Gel; these application site events were also most frequently considered treatment-related. The majority of AEs were graded as mild or moderate intensity; 3.2% of PEP005 Gel-treated patients and 1.6% of vehicle-treated patients had a severe AE.
- Analyses of selected AEs showed that:
    - Infections and infestations, as defined clinically by the investigators, were reported for 7.6% of PEP005 Gel treated patients and 5.5% of vehicle treated patients; the difference in incidence between treatment groups was not clinically meaningful, indicating that in spite of the increased incidence of skin-related AEs with PEP005 Gel treatment, these do not have a greater tendency to become infected.
    - Neoplasms were reported for a similar proportion of patients within the treatment groups, 3.0% vs. 2.7% for PEP005 Gel vs. vehicle, respectively. Basal cell carcinoma (1.5% vs. 1.1% for PEP005 Gel vs. vehicle) and SCC (0.9% vs. 0.8% for PEP005 Gel vs. vehicle) were the more frequently reported types of neoplasms. At the end of study (Day 57), the rate of SCC reported in the treatment area was comparable in patients treated with PEP005 Gel (0.3%, 3 of 1165 patients) and vehicle (0.3%, 2 of 632 patients). SCC in the treatment area was reported in no patients (0 of 184 patients previously treated with PEP005 Gel) in the 3 long-term follow-up studies.
    - Eye disorders occurred more frequently in patients treated with PEP005 Gel than patients treated with vehicle. Eyelid oedema and periorbital oedema were the most frequently reported eye-associated events. The majority of eye disorders were graded as mild or moderate and were generally considered related to study treatment.

- Cardiac disorders occurred with similar frequency between patients treated with PEP005 Gel (1.7%) and patients treated with vehicle (2.8%).

- SAEs were reported for 4.2% of PEP005 Gel-treated patients and 3.6% of vehicle-treated patients; the majority of SAEs were considered unrelated to study medication. There was one death that occurred in a patient treated with PEP005 Gel; the death was attributed to coronary artery atherosclerosis and hypertension and was considered by the investigator as unrelated to study medication.
- Very few patients (1 [0.1%] treated with PEP005 Gel and 2 [0.3%] treated with vehicle) discontinued from a study due to an AE; and 37 patients (all treated with PEP005 Gel [3.2%]) discontinued study medication, primarily due to application site reactions, but remained in the study for efficacy assessments.
- Following application of study medication, most PEP005 Gel-treated patients showed an increase in LSR scores relative to baseline, whereas most patients treated with vehicle showed no change from baseline LSR score. Local skin responses differed between treatment locations, with PEP005 Gel-treated areas on the face or scalp having a generally greater intensity than responses on the trunk or extremities. For the majority of patients treated with PEP005 Gel on the face or scalp, the maximum LSR score occurred on Day 4, which returned to baseline (or below) by Day 15. For the majority of patients treated with PEP005 Gel on the trunk or extremities, the maximum LSR score occurred between Days 3 and 8 and returned to baseline values (or below) by Day 29.
- The majority of patients who received field application of PEP005 Gel for the treatment of AK lesions showed no hypopigmentation, hyperpigmentation, or scarring at baseline or at the end of the study.
- There were no clinically meaningful changes in laboratory parameters, vital signs, or ECG assessments with PEP005 Gel treatment.
- Overall, PEP005 Gel was well tolerated in patients treated for AK lesions on the face/scalp and trunk/extremities. Patient compliance of the 2- or 3-day course of treatment was excellent, with 99% completing the regimen. Adverse events were transient and generally isolated to the application site.

6 BENEFITS AND RISKS CONCLUSIONS

6.1 CLINICAL BENEFIT OF TREATMENT WITH PEP005 GEL

For the Phase 3 studies, the complete clearance rates of PEP005 Gel, 0.015% on head locations were 37% and 47%, and for PEP005 Gel, 0.05% on non-head locations, the complete clearance rates were 28% and 42%. These results were statistically significant in comparison to vehicle gel ($p < 0.001$, for each study and for the pooled Phase 3 data for each location [head and non-head]). Although limitations exist when citing historical data for the topical products already approved to treat AK, the clearance rates seen in the PEP005 Gel Phase 3 studies are similar to rates reported with currently marketed products (15-58% for 5-FU; 34-47% for diclofenac; 26-46% for imiquimod). PEP005 Gel treatment, however, is efficacious after being applied for a substantially shorter duration. For head (face and scalp), PEP005 Gel, 0.015% is applied for three days and for non-head (trunk and extremities), PEP005 Gel, 0.05% is applied for only two days. In contrast, other products have longer durations of treatment. Treatment with 5-FU requires at least 3 to 4 weeks diclofenac requires 8 to 12 weeks, and imiquimod requires 4 weeks of treatment with efficacy assessment after the following 4-week off treatment period or 16 weeks of continuous treatment.(20,22,23,25,26,28,29,30)

Longer treatment durations reduce patient compliance.(13) Treatment compliance with the PEP005 Gel dosing regimen in the Phase 3 studies was 99%. Study medication discontinuation rates for all reasons are difficult to determine from the Phase 3 studies conducted in the approved products. However, the following discontinuation rates have been reported: 12% for 5-FU due to facial irritation(22) and 18% for diclofenac, mainly due to skin irritation and cutaneous reactions.(25,26) For imiquimod, rest periods during treatment were required (for Aldara®, 16% due to skin reactions, 3% due to treatment site infections and for Zyclara™, 11% due to adverse events overall) and 2% of patients discontinued due to skin reactions.(28,29,30)

PEP005 Gel applied topically at the concentrations used for treatment of AK lesions, has no systemic absorption, whereas, measurable plasma concentrations occur with use of 5-FU, diclofenac, and imiquimod.(20,22,26,28,29)

Based on the adequate and well controlled studies (PEP005-016 and PEP005-025 for head locations and PEP005-014 and PEP005-028 for non-head locations), PEP005 Gel demon-

strated efficacy. Taken collectively, the complete clearance rate (42% for the head locations and 34% for the non-head locations), the substantially shorter duration of treatment (two or three days), and the high treatment compliance (99% of patients) are evidence of a treatment advance for AK lesions.

After considering factors that impact duration of follow-up (ability to assess long term safety in an adequately controlled study, published data from other long term follow-up studies in AK, patient behaviour with regard to limiting sun exposure), a follow-up period of 12 months was selected for each of the long-term studies. At the 12 month follow-up, patient-based recurrence was 54% for head (face and scalp) locations and 56% for non-head (trunk and extremities) locations. These results are consistent with patient-based recurrence for imiquimod (42-67%) reported in a recent publication.(58) Lesion-based recurrence at 12 month follow-up was 13% for PEP005 Gel treated patients in each location (head and non-head). These findings are also consistent with lesion-based recurrence of 9% observed for imiquimod.(57).

6.2 CLINICAL RISKS ASSOCIATED WITH PEP005 GEL

Across all AK field treatment studies, 43% of patients treated with PEP005 Gel experienced an AE. Most AEs could be attributed to application site reactions and were typically considered related to treatment. Application site pruritus, application site pain, and application site irritation were the most frequently reported. Only 3.2% of PEP005 Gel-treated patients had a severe AE.

Treatment was well tolerated and discontinuation of treatment due to an AE occurred in only 3% of patients who received PEP005 Gel; discontinuation from the study occurred in 0.1% of patients. Serious AEs occurred at a low incidence (4% of PEP005 Gel patients) and most were unrelated to study medication. One death occurred in a PEP005 Gel-treated patient (due to coronary atherosclerosis and hypertension) and was considered unrelated to study medication.

When selected AEs of concern were reviewed, neoplasms such as BCC and SCC of the skin were infrequent, and occurred at similar incidences for PEP005 Gel and vehicle patients. Due to the low but serious risk of conversion to SCC, the Applicant commits to conduct a study in order to measure the long term outcome of SCC. Cardiac disorders also occurred at a low incidence with no difference between PEP005 Gel and vehicle. Infections were reported in 8% of PEP005 Gel patients and 6% of vehicle patients, showing no clinically meaningful difference between the groups and indicating that skin-related AEs with PEP005 Gel do not

have a greater tendency to become infected. Eye disorders, however, were seen more frequently in patients treated with PEP005 Gel (2.3% vs. 0.3% in vehicle patients).

Local skin responses were common with PEP005 Gel treatment; 95% of PEP005 Gel-treated patients showed an increase in LSR scores relative to baseline whereas most patients treated with vehicle showed no change from baseline LSR score. For patients treated on the face or scalp, the maximum LSR score occurred on Day 4, which returned to baseline values (or below) by Day 15. For patients treated on the trunk or extremities, the maximum LSR score occurred between Days 3 and 8, and returned to baseline values (or below) by Day 29.

For both treatment locations (face/scalp and trunk/extremities), erythema and flaking/scaling were the most common LSRs, followed by crusting and swelling. Local skin responses on the face and scalp generally were of greater intensity than responses on the trunk and extremities.

The majority of patients who received PEP005 Gel showed no hypopigmentation, hyperpigmentation, or scarring at baseline or the end-of-study assessments. No clinically meaningful changes in laboratory parameters, vital signs, or ECG assessments were seen with PEP005 Gel treatment.

No formal retreatment (repeat dosing) or simultaneous treatment studies were conducted in this clinical development programme. There were, however, 49 patients who received multiple treatments with PEP005 Gel. An assessment of AEs showed that these patients were not at higher risk for an AE or application site disorder with multiple treatments of PEP005 Gel. For the assessment of LSRs, there were too few patients for meaningful interpretation.

As summarised above, localised application site disorders (pruritus, pain, irritation) and local skin responses, particularly erythema, flaking, and scaling are the main characteristics of the safety profile of PEP005 Gel. These local adverse events are transient, and typically resolve without sequelae within 2-4 weeks of application. Additionally, PEP005 Gel is not systemically absorbed. Comparator products also report local skin responses but these appear more intense and several products recommend “rest-periods” when severe skin reactions are experienced (imiquimod and 5-FU). Comparator products also report systemic absorption when applied topically and systemic adverse events such as flu-like symptoms and fatigue (imiquimod). Therefore, the risks associated with the safety profile of PEP005 Gel appear reduced compared to that of marketed treatments.

6.3 CONCLUSIONS

The following summarise the benefits and risks of using PEP005 Gel to treat AK:

- PEP005 Gel is efficacious in the treatment of AK with complete clearance rates of 42% for the face and scalp (95% confidence interval of 36.4, 48.3) and 34% for the trunk and extremities (95% confidence interval of 27.9, 40.6).
- The short duration of treatment (2 to 3 days) provides an advance for treatment compliance and patient convenience.
- PEP005 Gel has no detectable systemic absorption even at concentrations applied topically which are effective for complete clearance of AK lesions.
- At the 12 month follow-up, patient-based recurrence was 54% for head (face and scalp) locations and 56% for non-head (trunk and extremities) locations. Lesion-based recurrence at 12 month follow-up was 13% for each (head and non-head locations).
- Localised application site disorders (pruritus, pain, irritation) and local skin responses, particularly erythema, flaking, and scaling are the main characteristics of the safety profile of PEP005 Gel. These local adverse events are transient, and typically resolve without sequelae within 2 weeks of application to the face or scalp and within 4 weeks of application to the trunk or extremities. Furthermore, these local events do not have a tendency to become infected, do not cause scarring, and do not change pigmentation.
- No formal retreatment (repeat dosing) studies were conducted, however, 49 patients received multiple treatments with PEP005 Gel. Safety risks, in general, did not appear to be higher in these patients.
- PEP005 Gel has a shorter duration of treatment compared to other products and it is considered to offer comparable short term efficacy. With the shorter duration of treatment, efficacy with PEP005 Gel is achieved more rapidly following study medication application. The risks associated with the safety profile of PEP005 Gel appear reduced compared to that of marketed treatments. Overall the risk-benefit profile of PEP005 Gel is considered favourable.

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