Common Drug Review
Clinical Review Report

April 2017

Drug	5-fluorouracil 0.5% and salicylic acid 10.0% (Actikerall)
Indication	Indicated for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) of the face, forehead, and balding scalp in immunocompetent adult patients
Reimbursement request	As per indication
Dosage form (s)	Topical solution
NOC date	August 28, 2015
Manufacturer	Cipher Pharmaceuticals Inc.

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ABBREVIATIONS

5-FU	5-fluorouracil
AE	adverse event
AK	actinic keratosis
BCC	basal cell carcinoma
CI	confidence interval
DB	double blind
EMEA	European Medicines Agency
FDA	Food and Drug Administration
ITT	intention-to-treat population
LOCF	last observation carried forward
NMSC	non-melanoma skin cancer
PP	per-protocol
RCT	randomized controlled trial
RR	relative risk
SA	salicylic acid
SAE	serious adverse event
SCC	squamous cell carcinoma
SD	standard deviation

EXECUTIVE SUMMARY

Introduction

According to the British Association of Dermatologists, 15% to 25% of actinic keratosis (AK) lesions spontaneously resolve during a one-year period.[1] However, AK lesions may develop into invasive squamous cell carcinoma (SCC) if left untreated.[2] The rate of progression from AK to SCC is unknown. Mathematical models derived from a study predicted that for an individual with an average of 7.7 AKs, the probability of developing an SCC at the same or nearby site within a 10-year period is approximately 10.[3] The risk of malignant transformation is higher in patients who are immunocompromised. In Canada, 74,100 new cases of non-melanoma skin cancers (NMSCs) and 270 deaths due to these cancers were predicted for 2011.[2]

AK typically manifests as 2 mm to 6 mm scaly macules, papules, or plaques that are skin to reddish-brown in colour, and may be flat or thickened (hyperkeratotic).[4,5] Patients with AK are usually referred to dermatologists and diagnosis is frequently made on clinical appearance alone.[1] A skin biopsy may be required when there is clinical doubt or suspicion of invasive malignancy.[1,5] Detectable AK may be associated with a field change where the surrounding skin is also altered and subclinical lesions may be present.[2] Patient input to the CADTH Common Drug Review (CDR) suggests that cosmetic issues are a major concern for patients, and this can have a negative impact on self-confidence.

The submitted product is a combination of two topical therapies, 5-fluorouracil 0.5% (5-FU) and salicylic acid 10% (SA). 5-FU is an antimetabolite that is already approved as monotherapy for treatment of AK, although at a concentration of 5%. SA is a keratolytic, and the theory behind its use is to improve penetration of the combination in hyperkeratotic AK. The 5-FU/SA combination under review is administered once daily to affected lesions, until lesions have cleared or for a maximum of 12 weeks. It is indicated for the management of grade I/II hyperkeratotic AK.

Indication under review
Indicated for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) of the face, forehead, and balding scalp in immunocompetent adult patients
Listing criteria requested by sponsor
As per indication

The objective of this report was to perform a systematic review of the beneficial and harmful effects of 5-FU (0.5%) combined with SA 10% applied topically once daily for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) of the face, forehead, and balding scalp in immunocompetent adult patients.

Results and Interpretation

Included Studies

One pivotal, multi-centre, double-blind, randomized, controlled trial (DB RCT), Study 0702, met the inclusion criteria for this review. Study 0702 was designed to test the non-inferiority of 5-FU/SA to diclofenac gel and its superiority to placebo in patients with hyperkeratotic (grade I/II) AK. A total of 470 patients were randomized 2:2:1 to 5-FU/SA, diclofenac gel, or placebo. For the purpose of this review,

only comparisons between 5-FU/SA and placebo were reviewed, as diclofenac gel is not an approved therapy for AK in Canada. Patients self-applied study drug daily to target areas until lesions had cleared or a maximum of 12 weeks, and assessments were carried out at end of treatment and eight weeks post-treatment. The target areas were the face/forehead (A) and bald scalp (B), and the overall treatment area contained at least four and no more than 10 distinct AK lesions, with a distance of at least one centimetre between lesions, and a maximum lesion diameter of 1.5 cm^2. The primary outcome of the study was the proportion of patients with complete histological clearance of their pre-defined AK target lesion, at eight weeks post-treatment. Secondary outcomes included assessments of changes from baseline in lesion count, lesion area, lesion response (complete or partial, stable or progressive), as well as physician and patient assessments of efficacy and tolerability.

Critical appraisal issues included the challenges in maintaining blinding with a large difference in proportion of 5-FU/SA patients experiencing adverse events that are associated with the use of this type of therapy. The manufacturer also does not appear to have accounted for multiple comparisons in their statistical analyses. Patients self-administered their topical therapy, and therefore, there may have been variability in administration of study drug. Those in the 5FU/SA group also administered less drug on average than those in the placebo group, indicating that tolerability issues may have had an impact on patient's application of the study drug. The primary outcome focused on clearance of a single pre-defined target lesion, yet it was unclear how this lesion was chosen, and given that AK can spontaneously resolve (as evidenced by the high response rate in the placebo group) relying on a single lesion for assessment of the primary outcome may be problematic. Issues that may have had an impact on external validity included the lack of patients with AK on the backs of their hands, the lack of active comparators with approved therapies for AK, and the fact that the entire study was carried out in one country; Germany.

Efficacy

Complete histological clearance of AK in a single pre-defined target lesion at eight weeks post-treatment was the primary outcome of the study. Complete clearance of this AK lesion was achieved in 70% of patients treated with 5-FU/SA versus 43% of patients treated with placebo, and therefore 5-FU/SA was statistically superior to placebo for the primary outcome (difference between groups [97.5% CI for the difference between groups] of 0.27 [0.13 to 0.40], $P < 0.001$). There were a larger proportion of lesions cleared at end of treatment in the 5-FU/SA group compared with placebo (50% versus 33% of lesions cleared) and this difference was statistically significant ($P < 0.05$). Clinical response was assessed as a secondary outcome, and there was a higher proportion of 5-FU/SA patients with a complete response at eight weeks post-treatment compared with placebo (55% versus 15% of patients) and this difference between groups was statistically significant ($P < 0.00001$). The proportion of patients with partial response was 42% with 5FU/SA and 67% with placebo. The population in this study included both patients with grade I (non-hyperkeratotic) and grade II (hyperkeratotic) AK, and no subgroup analysis was performed by the manufacturer, therefore it is unknown whether this combination of 5-FU/SA will be more efficacious in one population versus the other. Among key secondary outcomes for this review, quality of life was not assessed using a validated instrument, and this lack of quality of life data is an important limitation in a condition characterized by significant quality of life issues, as described in patient input to CDR.

Patient assessment of clinical improvement was a secondary outcome, and a larger proportion of patients treated with 5-FU/SA rated their outcome as very good or good (83% versus 72% of patients) when compared with placebo, and this difference was statistically significant ($P < 0.00001$).

Recurrence of target lesions was assessed at both six months and 12 months of follow up. Of the 742 cleared lesions in the 5-FU/SA group, 8% had recurrence, while of the 189 lesions cleared in the placebo group, 14% recurred. This difference in recurrence rate between groups was statistically significant (Wilcoxon test, *P* = 0.02347). At 12 months follow up, 14% of lesions in the 5-FU/SA group had recurred while 20% of lesions in the placebo group had recurred, and this difference was statistically significant (*P* = 0.04419).

Harms

Of the patients included who experienced and adverse event (AE), 95% were treated with 5-FU/SA and 85% were treated with placebo. The most common AE were local skin reactions such as inflammation (73% in 5FU/SA versus 36% placebo), irritation (86% versus 61%) and pruritis (45% versus 41%). Of these, when focusing on just the AE that were classified as severe, the numerical differences between groups is larger, for inflammation (16% in 5FU/SA versus 1% placebo), irritation (21% versus 3%), pruritus (7% versus 0%).

Serious adverse events occurred in only 1% of 5-FU/SA patients and 4% of patients treated with placebo. No single serious AEs occurred in more than one patient.

Withdrawals due to AE occurred in 4% of patients treated with 5-FU/SA and 3% of patients in the placebo group. The most common reason for withdrawal due to AE with 5-FU/SA was “application site disorder.”

Notable harms of interest for this review included application site scarring and pigment changes, and there were none of these events reported in in either the 5-FU/SA groups or placebo.

Potential Place in Therapy

This information is based on that provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

5-FU/SA is an addition to currently available topical drugs for the treatment of individual clinical grade I/II (slightly palpable and moderately palpable) lesions. The manufacturer claims that the combination of 5-FU/SA is more effective for hyperkeratotic lesions, but evidence for an advantage of 5-FU/SA compared with the other topical drugs in this population is lacking.

As current treatments can be used to treat grade I and II AK lesions, it is unclear what the place in therapy for 5-FU/SA is. Therefore, the clinical expert consulted by CDR stated that 5-FU/SA would not fulfill any unmet need in therapy.

Conclusions

One DB RCT that was designed to compare 5-FU/SA with placebo and diclofenac gel met the inclusion criteria for this review. The primary outcome of Study 0702 was the proportion of patients with complete clearance of a single pre-defined target AK lesion eight weeks after end of treatment, and 5-FU/SA was statistically significantly superior to placebo for this end point. Other end points related to AK clearance, including number of lesions cleared, were also statistically significantly improved for 5-FU/SA versus placebo. Quality of life was not assessed; therefore, no conclusions can be drawn regarding the effects of 5-FU/SA on quality of life. Surveys found that the majority of patients rate clinical improvement with their therapy as “good” or “very good,” and this was statistically significant versus placebo, although no adjustment was made for multiple comparisons, and the clinical significance of this

difference versus placebo is uncertain. There were no consistent reports of specific serious adverse events noted with use of 5-FU/SA after 12 weeks of treatment, and tolerability issues were predictable adverse effects of this topical combination: inflammation, erythema, and irritation.

TABLE 1: SUMMARY OF RESULTS

	Study 0702		
	5-FU/SA N=187	**PLACEBO N = 98**	**Statistical Analyses 5-FU/SA Versus Placebo**
Complete Histological Clearance of Target Lesion (Primary End Point)			
Participants at week 20, N (%)			
No AK in target lesion	124 (70)	41 (43)	
AK still present	50 (28)	51 (53)	
Missing result	3 (2)	4 (4)	
Difference between groups [97.5% CI]			*0.27[a] [0.13 to 0.40]* *P = 0.000019*
Number of lesions cleared			
Mean (SD) lesions per patient, baseline	5.8 (NR)	5.5 (NR)	
Mean (SD) lesions per patient, end treatment (week 12)	2.8 (NR)	3.7 (NR)	*P = 0.00062[b] (one-sided)*
Mean (SD) lesions per patient, post-treatment (week 20)	1.4 (NR)	3.5 (NR)	
Proportion of lesions cleared overall, week 12, n (%)	507/1014 (50)	177/532 (33)	*P* < 0.05
Response – Post Treatment (Week 20)			
Progressive disease	0	1 (1)	*P < 0.00001[c] (one-sided)*
Stable disease	4 (2)	16 (17)	
Partial response	74 (42)	62 (67)	
Complete response	97 (55)	14 (15)	
Harms			
Participants with > 0 SAEs, N (%)	2 (1)	4 (4)	
Participants with > 0 AEs, N (%)	178 (95)	83 (85)	
WDAEs, N (%)	7 (4)	3 (3)	
Application site scarring	0	0	

AE = adverse event; AK = actinic keratosis; CI = confidence interval; 5-FU = fluorouracil (0.5%); SA = salicylic acid; SAE = serious adverse event; SD = standard deviation; WDAEs = withdrawal due to adverse events.
Complete response = participants with all lesions cleared.
[a] Point estimate calculated by CDR.
[b] Wilcoxon: Z-value.
[c] Cochran-Armitage Trend Test – Full analysis set (comparison of complete responders versus non-complete responders).

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

According to the British Association of Dermatologists, 15% to 25% of actinic keratosis (AK) lesions spontaneously resolve during a one-year period.[1] However, AK lesions may develop into invasive squamous cell carcinoma (SCC).[2] The rate of progression from AK to SCC is unknown. Mathematical models derived from a study predicted that for an individual with an average of 7.7 AKs, the probability of developing a SCC at the same or nearby site within a 10-year period is approximately 10%.[3] The risk of malignant transformation is higher in patients who are immunocompromised. In Canada, 74,100 new cases of non-melanoma skin cancers (NMSCs) and 270 deaths due to these cancers were predicted for 2011.[2]

AK typically manifests as 2 mm to 6 mm scaly macules, papules, or plaques that are skin to reddish-brown in colour.[4,5] Patients with AK are usually referred to dermatologists and diagnosis is frequently made on clinical appearance alone.[1] A skin biopsy may be required when there is clinical doubt or suspicion of invasive malignancy.[1,5] Detectable AK may be associated with a field change where the surrounding skin is also altered and subclinical lesions may be present.[2] Patient input to CDR suggests that cosmetic issues are a major concern for patients, and this can have a negative impact on self-confidence. The clinical expert on this review also noted that the cosmetic issues can be particularly problematic for patients who work with the public, and this includes not only the lesions on the face but lesions that occur on the back of the hands. The cosmetic issues not only arise from the original lesions, but also the results of topical therapy, which can lead to inflammation, redness, crusting, blistering, and/or weeping at the site of treatment.

1.2 Standards of Therapy

No Canadian guidelines currently exist for the treatment of AK. The choice of treatment is generally guided by the clinical presentation of the condition and may include general measures such as sun protection.[6]

Treatment options for AK in Canada can be divided into two categories: lesion-directed therapies and field-directed therapies. Lesion-directed therapies include cryotherapy, surgical excision, curettage, and laser therapy.[4] Field-directed therapies include photodynamic therapy, chemical peels, imiquimod cream (5%, 3.75%, or 2.5%), topical 5-fluorouracil (5-FU) 5% cream, and ingenol mebutate gel 0.05% and 0.015%.[4]

Lesion-directed therapies are often used to treat isolated lesions that are few in number, with cryotherapy being a widely used method according to the clinical expert. Field-directed therapies may be used to treat extensive areas of affected skin or multiple lesions. Field-directed therapies can treat both visible and non-visible lesions in the actinic field and have the advantage of being noninvasive, with certain treatments that can be administered by the patient. Current approaches to the management of AK use both lesion-directed and field-directed methods as a strategy to increase the overall success of treatment.[7]

1.3 Drug

The submitted product is a combination of two topical therapies, 5-FU 0.5% and salicylic acid 10% (SA). 5-FU is an antimetabolite that is already approved as monotherapy for treatment of AK, although in that case at a concentration of 5%. SA is a keratolytic, and the theory behind its use is to improve penetration of the combination in hyperkeratotic AK. The 5-FU/SA combination under review is administered once daily to affected lesions, until lesions have cleared or for a maximum of 12 weeks. It is indicated for the management of grade I/II AK.

Indication under review
Indicated for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) of the face, forehead, and balding scalp in immunocompetent adult patients
Listing criteria requested by sponsor
As per indication

TABLE 2: KEY CHARACTERISTICS OF 5-FU/SA, INGENOL MALEATE, 5-FU, IMIQUIMOD

	5-FU/SA	Ingenol mebutate	5-FU	Imiquimod
Mechanism of Action	5-FU: Competitive antagonist for uracil in formulation of RNA SA: Keratolytic	Unknown (cytotoxic and inflammatory mechanisms)	Competitive antagonist for uracil in formulation of RNA	Immune response modifier
Indication[a]	Slightly palpable and/or moderately thick hyperkeratotic AK (grade I/II) of the face, forehead, and balding scalp in immunocompetent adult patients	Non-hyperkeratotic, non-hypertrophic AK	Premalignant keratosis and superficial BCC	Clinically typical, non-hyperkeratotic, non-hypertrophic AK on the face or balding scalp
Route of Administration	Topical solution of 5-FU 0.5% and SA 10%	Topical, 0.05% and 0.015% gel	Topical, 5% cream	Topical, 5%, 3.75%, and 2.5% cream
Recommended Dose	Applied to actinic keratosis in an area of up to 25 cm^2 once daily until the lesions have completely cleared or for up to a maximum of 12 weeks	Trunk and extremities: 0.05% gel once daily for 2 consecutive days Face and scalp: 0.015% gel once daily for 3 consecutive days	Twice daily for 2 to 4 weeks	Face or balding scalp 5% cream: twice weekly for 16 weeks 3.75% or 2.5% cream: once daily for 2 treatment cycles of 2 weeks each separated by a 2-week no-treatment period
Serious Side Effects / Safety Issues	None reported	None reported	None reported	None reported

	5-FU/SA	Ingenol mebutate	5-FU	Imiquimod
Recommended Treatment Area	up to 25 cm^2	0.05% and 0.015% gel: 25 cm^2 Clinical data on treatment of more than one area are not available.	Entire affected area No maximum recommended treatment area is suggested.	5% cream: 25 cm^2 (safety applied to areas greater than 25 cm^2 for the treatment of AK has not been established.) 3.75% or 2.5% cream: up to 200 cm^2 (safety and efficacy applied to a larger area has not been established.)

[a] Health Canada indication.
AK = actinic keratosis; 5-FU = fluorouracil (0.5%); RNA = ribonucleic acid; SA = salicylic acid.
Source: Product Monographs for 5FU, imiquimod and ingenol from e-CPS[8], and Product Monograph for 5FU/SA from submission.[9]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of 5-FU combined with SA 10% applied topically once daily for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) of the face, forehead, and balding scalp in immunocompetent adult patients.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Immunocompetent adult patients with slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) of the face, forehead, and balding scalp
Intervention	Fluorouracil 0.5% combined with salicylic acid 10%, applied topically once daily up to a maximum of 12 weeks
Comparators	Ingenol mebutate topical gel 5-fluorouracil cream, 5% Imiquimod cream, 5%, 3.75%, or 2.5%
Outcomes	**Key efficacy outcomes:** Complete clearance of AK lesions[a] Partial clearance of AK lesions[a] Reduction in number of AK lesions[a] Health-related quality-of-life (e.g., SF-36 or any valid scale) [a] **Other efficacy outcomes:** Recurrence of AK lesions[a] Progression to SCC[a`] Patient satisfaction[a] **Harms outcomes:** AEs SAEs WDAEs Mortality LSRs Pigmentation changes, and scarring
Study Design	Published and unpublished Phase III RCTs

AE = adverse event; AK = actinic keratosis; DB = double blind; LSR = local skin response; RCT = randomized controlled trial; SAE = serious adverse event; SCC = squamous cell carcinoma; SF-36 = short form health survey; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Actikerall (5-fluourouracil and salicylic acid) and keratosis.
No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on September 27, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on February 15, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings from the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4: Details of Included Studies and described in Section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

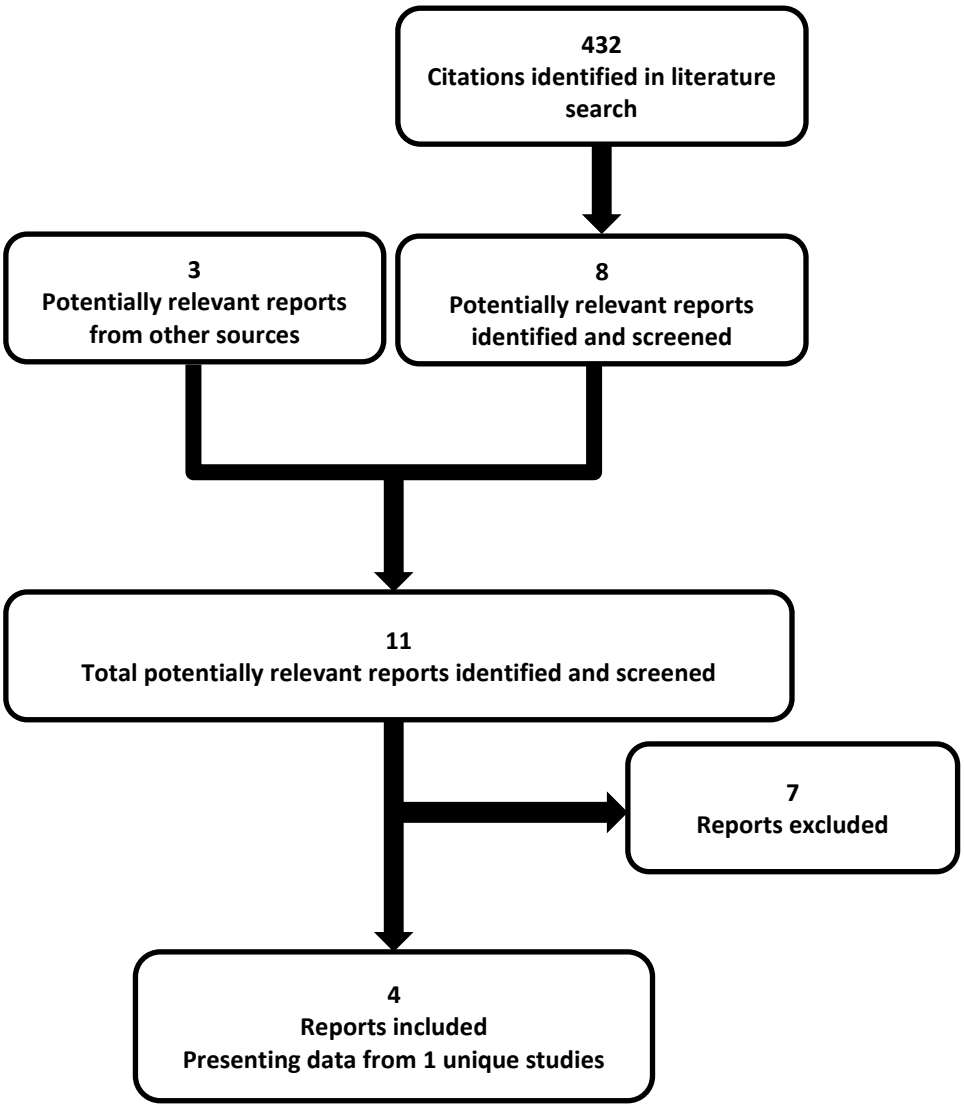

TABLE 4: DETAILS OF INCLUDED STUDIES

		Study 0702
DESIGNS AND POPULATIONS	**Study Design**	DB RCT
	Locations	Germany: 38 centres
	Randomized (N)	470
	Inclusion Criteria	Female or male participants aged between 18 and 85 years inclusive and suffering from 4 to 10 AK lesions grade I and II (according to Olsen 1991) in their face and forehead or on their bald scalp. The summarized test area of all single AK lesions was not to cover a total area of more than 25 cm^2 (including a 5 mm to treat surrounding area).
	Exclusion Criteria	Had received treatment of AK within the treatment area (face / scalp) in the three months preceding this clinical trial. Known hypersensitivity to 5-FU or SA, or acetylsalicylic acid Current other malignant or benign tumours of the skin within the treatment area (e.g., malignant melanoma, basal cell carcinoma, squamous cell carcinoma)
DRUGS	**Intervention**	5-FU (0.5%) in combination with SA 10% solution applied topically once daily
	Comparator(s)	Vehicle applied topically once daily or Comparator gel containing diclofenac sodium 3% HA applied topically twice daily
DURATION	**Phase**	
	Run-in	NR
	Double-blind	20 weeks (12 weeks treatment)
	Follow up	12 months post-treatment
OUTCOMES	**Primary End Point**	Histological clearance of one pre-defined AK lesion at 8 weeks post-treatment
	Other End Points	Lesion count Lesion grading Lesion area Investigator/participant assessment of efficacy
NOTES	**Publications**	Stockfleth 2011[10]

AK = actinic keratosis; 5-FU = fluorouracil (0.5%); HA = hyaluronic acid; NR = not reported; SA = salicylic acid.
Note: 3 additional reports were included (Health Canada reviewers report,[11] manufacturer submission,[12] CSR for Study 0702[13]).
Source: CSR for Study 0702.[13]

3.2 Included Studies

3.2.1 Description of studies

One pivotal multi-centre DB RCT, Study 0702, met the inclusion criteria for this review. Study 0702 was designed to test the non-inferiority of 5-FU/SA to diclofenac gel and its superiority to placebo in patients with hyperkeratotic (grade I/II) AK. A total of 470 participants were randomized 2:2:1 to 5-FU/SA, diclofenac gel, or placebo. No stratification factors were reported. For the purpose of this review, only comparisons between 5-FU/SA and placebo were reviewed, as diclofenac gel is not an approved therapy for AK in Canada. Participants self-applied study drug daily to target areas until lesions had cleared or a maximum of 12 weeks, and assessments were carried out at end of treatment and eight weeks post-treatment. The target areas were the face/forehead (A) and bald scalp (B), and the overall treatment area contained at least four and no more than 10 distinct AK lesions, with a distance of at least one centimetre between lesions, and a maximum lesion diameter of 1.5 cm.[2] The primary outcome of the study was the proportion of patients with complete histological clearance of their pre-defined AK target lesion, at eight weeks post-treatment. Secondary outcomes included assessments of changes from baseline in lesion count, lesion area, lesion response (complete/partial/stable/progressive), as well as physician and patient assessments of efficacy and tolerability.

3.2.2 Populations

a) Inclusion and exclusion criteria

Adult patients were included if they had grade I/II AK on their face, forehead or bald scalp, with between four and 10 lesions, and a total affected area of not more than 25 cm^2 (Table 4).

b) Baseline characteristics

Patients enrolled were on average 72 years old, predominantly (85%) male, and all were Caucasian (Table 5). These demographic characteristics are consistent with the population that would be expected to use 5-FU/SA according to the clinical expert consulted by CDR. The most common site of involvement was the face/forehead (48% of patients), and a small proportion of patients had involvement of both the face/forehead and bald scalp. Approximately one-third of patients had grade I AK, while about 63% had grade II, and a small proportion (approximately 7%) had grade III.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

	5-FU/SA N = 177	PLACEBO N = 96
Mean age	71.8 (6.8)	72.3 (6.0)
Male, n (%)	152 (86)	81 (84)
Caucasian, n (%)	187 (100)	98 (100)
Mean duration of AK, years	4.9	5.5
Previous nonsurgical therapy, n (%)	128 (68)	69 (70)
Previous surgical therapy	30 (16)	15 (15)
Mean (SD) lesions per patient	5.8 (1.6)	5.6 (1.5)
Mean (SD) total lesion area per participant, mm^2	355.9 (128.9)	341.4 (132.9)
Location of lesions:		
• bald scalp	65 (35)	33 (34)
• face (forehead)	92 (49)	47 (48)
• bald scalp and face	30 (16)	18 (18)

	5-FU/SA N = 177	PLACEBO N = 96
Biopsy diagnosis, grade[a], n (%)		
AK I	60 (32)	29 (30)
AK II	112 (60)	64 (65)
AK III	15 (8)	5 (5)

AK = actinic keratosis; 5-FU = fluorouracil (0.5%); SA=salicylic acid; SD = standard deviation.
[a] Grade: 0 means no AK lesion present, neither visible nor palpable; grade I means mild flat, pink maculae, no hyperkeratosis nor erythema, slight palpability, with AK felt easier than seen; grade II means moderate pink to reddish papules and erythematous plaques with hyperkeratotic surface, moderately thick AK that are easily seen and felt; grade III means severe, very thick, and/or obvious AK.
Source: CSR for Study 0702.[13]

3.2.3 Interventions

The 5-FU/SA solution was topically applied once daily to the AK lesions. Placebo solution was topically applied once daily to the AK lesions. The study drugs were applied using the supplied brush applicator to each target lesion and a surrounding area of approximately 5 mm to treat surrounding subclinical parts of the AK lesions. Generally 0.5 g of solution covered an overall area up to 25 $cm.^2$ If severe adverse events (SAEs) occurred, the frequency of 5-FU/SA or placebo application could be reduced to three times per week. Throughout the dosing period, patients were not to miss application on more than one day per week, i.e., one dose of 5-FU/SA or placebo.

3.2.4 Outcomes

a) Primary outcome

The primary end point was to show superiority of 5-FU treatment to placebo measured by histological clearance of one pre-selected target lesion, at eight weeks post-treatment. The biopsy was performed at a representative lesion defined at the screening visit. It is unclear how this target lesion was chosen, among the various AK lesions in a given patient. The assessment was categorized into either "cleared" or not "cleared" at this eight week post-treatment visit.

Lesion response

The clearance rate (complete/partial) of AK lesions (determined by clinical evaluation) in the treatment area (target Areas A and B) were measured by comparing the total AK lesion counts pre-treatment (day 1 before study drug application) with the lesion counts measured throughout this clinical trial up to the eight weeks post-treatment visit. At each of these visits the investigator counted the number of clinically typical, visible AK lesions in the treatment area, i.e., face and forehead (target area A) and bald scalp (target area B). The number of lesions in both areas was summarized. The final evaluation for determination of complete/partial clearance was done at the eight weeks post-treatment visit. To evaluate the development of AK lesions and to follow up the healing process during drug treatment, lesion counts were also performed at each visit. A complete response in a given patient was defined as complete clearance of AK lesions in that patient.

Patient satisfaction with treatment was assessed using a patient-reported outcome, the patient overall assessment of clinical improvement. An assessment was performed by the patient in week 6, at the end of treatment, and at the eight weeks post-treatment visit and contained the following items:

a) clinical improvement assessment:
The improvement of the lesions was assessed as:

- very good
- good
- minimal
- none
- worsening.

b) assessment of tolerability:
The tolerability was assessed for:

- inflammation
- itching
- burning
- pain

using none, little, moderate, strong and very strong.

For the above, the proportion of patients falling under each category were reported (e.g., proportion of patients with "very good/good" improvement; the proportion of patients with "very strong" inflammation), rather than using a scoring system.

3.2.5 Statistical analysis

The primary end point was to show superiority of 5-FU treatment to placebo measured by histological clearance of one pre-selected target lesion, at eight weeks post-treatment. The primary study hypotheses was analyzed with the Chi-Square test at significance level of $\alpha = 0.025$ for a 1-sided test. The following hypothesis was tested for superiority:

> $H_{0,1}$: The rate of patients with "cleared" lesions" under placebo treatment was higher or equal compared with the rate under 5-FU/SA-treatment.
> This hypothesis is expressed mathematically by:
> H_0: PL ≥ 5-FU/SA versus H_1: PL < 5-FU/SA.

Two-sided tests were performed for testing of secondary efficacy outcomes. For the secondary outcomes, the changes from baseline for each visit (visits 3 to 7) were analyzed. The manufacturer noted that frequencies of patients for secondary target variables were compared between treatment groups by Chi-Square-tests, however no further details were provided. Lesion counts at end of study was compared by Wilcoxon-Mann-Whitney- tests between treatment groups. The patient's overall assessment of efficacy and tolerability was compared between treatment groups by Cochran-Armitage test for trend.

A hierarchical approach was taken for analysis of the primary outcome, such that superiority versus placebo was tested first, and if achieved, non-inferiority to the diclofenac comparator was then tested. There does not appear to have been any other attempts to account for multiple comparisons, either for multiple comparisons due to multiple treatment groups (placebo, diclofenac) or for testing of multiple secondary outcomes.

The sample size estimation for the test on superiority to placebo was based on the following assumptions:

- The rate of responders with respect to histological clearance of the target lesion was estimated to be:
  - 30% at a maximum for treatment with placebo
  - approximately 55% for treatment with 5-FU/SA
- the significance level was set to a = 0.025 for a one-sided test
- the power was to be at least 80%.

No further details were provided by the manufacturer regarding how these estimates were arrived at. Under these assumptions the sample size available for analysis was calculated to be N = 60 in each treatment group. Adding an expected dropout rate of 15% gave a total sample size of N = 69 patients to be randomized in each treatment group.

For the primary outcome, patients with missing histological data were classified as “not cleared.” The primary time point for analysis of the secondary efficacy variables was the last visit conducted for a given patient — usually the values at visit 12 weeks after start of treatment; or if the patient prematurely discontinues the treatment, the last available data (last observation carried forward [LOCF] value).Missing data for other visits (visit 3, 4, 5 and 6) were replaced by the last available observation for this variable.

a) Analysis populations

PPS "Per protocol set:" The patient adhered reasonably well to this study protocol without relevant protocol deviations or violations. Patients who dropped out of the study because of therapeutic failure (insufficient efficacy of treatment), therapeutic success (no further treatment necessary), complications of the study disease, or adverse events (AEs) were classified in the "per protocol set," if no other relevant protocol deviations or violations had occurred and the patients used study medication for an interval of at least 64 days or until clearance of all lesions.

FAS "Full analysis set:" All patients in whom the study diagnosis was confirmed and for whom data on efficacy variables after use of the study medication were available and who used study medication for more than 12 days, were classified in the "full analysis set" regardless of any protocol deviations or violations.

Safety "Safety set:" All patients who applied at least one dose of the study medication and for whom any data or information about the time after the first dose of study medication were available.

3.3 Patient Disposition

The proportion of patients who withdrew from the study was 8% with 5-FU/SA and 5% with placebo (Table 6). AEs were the most common reason for withdrawal.

TABLE 6: PATIENT DISPOSITION

	Study 0702	
	5-FU/SA N = 187	PLACEBO N = 98
Screened, N	510	
Randomized, N (%)	187	98
Randomized and treated, n (%)	187	98
Discontinued, N (%)	14 (8)	5 (5)
• Adverse event	7 (4)	3 (3)
• Lack of tolerability	1 (1)	0
• Lost to follow up	1 (1)	0
• Other (e.g., withdrawn consent)	5 (3)	2 (2)
FAS, N	177 (95)	96 (98)
PP, N	168 (90)	87 (89)
Safety, N	187 (100)	98 (100)

FAS = full analysis set; 5-FU = fluorouracil (0.5%); PP = per protocol; SA = salicylic acid.
Source: CSR for Study 0702.[13]

3.4 Exposure to Study Treatments

In the case of SAEs, the patients were allowed to reduce the frequency of medication application from daily to three times weekly (described as a "dose reduction"). The number of patients who underwent dose reduction was higher in the 5-FU/SA group (62 patients, 34%) versus the placebo group (10 patients, 10%).

Compliance was calculated as the difference in days between the days scheduled and the actual treatment days. According to the diary entries most patients had a compliance of 80% to 120% (86.1% of the patients in the placebo group and 85.0% in the 5-FU/SA group). A compliance rate of < 80% was observed for nine patients in the 5-FU/SA group and for no patient in the placebo group. Diaries were not available from 33 patients; mainly these were patients who dropped out prematurely and did not return for a post-study follow up. The mean amount of 5-FU/SA applied by the patients was 16.9 g, and patients randomized to placebo applied 28.5 g. Differences between the amounts of placebo and 5-FU/SA can be attributed to the number of patients, who reduced the dose during the study and the time of dose reduction (16.5% of the patients in the 5-FU/SA group reduced dose already at week 3; whereas, at the same time only 3.1% of the patients in the placebo group had reduced the dose).

3.5 Critical Appraisal

3.5.1 Internal validity

Study 0702 was identified as a double-blind RCT by the manufacturer, and the placebo group employed a similar vehicle to the 5-FU/SA. The nature of the AE profile of 5-FU/SA could have potentially compromised blinding, and AEs that one would expect to occur more commonly in the 5-FU/SA group, such as irritation and inflammation, were indeed much more frequent in this group than in the placebo comparator. This may have led to ascertainment bias, with patients and investigators being able to accurately speculate as to which group they had been assigned. Additionally, the difference in local skin reactions might have had a negative impact on adherence to the study drug, and adherence appeared to be lower with 5-FU/SA than with placebo, according to measures of the amount of study drug used by each group.

Randomization was carried out using an external body and steps appear to have been taken to maintain allocation concealment. No stratification factors were identified however. Power calculations were performed, although the rationale behind the assumptions made in these calculations was not provided.

The primary outcome in the included study was the proportion of patients with histological clearance of a single target AK lesion at 12 weeks post-treatment. The target lesion was chosen at baseline, yet there was no indication of how this lesion was chosen compared with the other AK lesions, as each patient was to have had at least four and no more than 10 AK lesions at baseline. Although the number of AK lesions that could reasonably be biopsied for histological analysis is clearly limited in a given patient, relying on a single lesion for assessment of the primary outcome makes it difficult to evaluate the true effect of the test drug. As noted by the high proportion of responders in the placebo group, AK lesions can spontaneously clear; therefore, relying on a single lesion increases the risk of lesion clearance occurring purely by chance alone rather than the effect of the intervention.

It is unclear how the manufacturer accounted for multiple statistical comparisons when assessing these outcomes in the study. Comparisons were carried out between the intervention, 5-FU/SA, and both diclofenac gel and placebo, and these comparisons were also carried out for each of the primary and secondary outcomes. Accounting for multiplicity is often carried out using a hierarchical testing procedure; however, the manufacturer appears to have only employed hierarchical testing for the primary outcome. The threshold for statistical significance for all the secondary outcomes appears to have been maintained at $P < 0.05$; therefore, adjustments were also not made to the threshold for statistical significance.

All study drugs were self-applied by patients, after an initial training session with their first dose, and this might have resulted in variability in the accuracy of application, impacting both efficacy and harms. The study drugs were applied using the supplied brush applicator to each target lesion and a surrounding area of approximately 5 mm to treat surrounding subclinical parts of the AK lesions. Given that patients would normally be expected to self-administer these topical therapies, this approach to design is not unreasonable, however it does call into question whether some of the differences in efficacy and harms between study groups may have been due to accuracy and consistency of the patient in applying study medication. Application site reactions such as inflammation and pain might also have an impact on patient adherence, as patients may have applied less of the study drug or to a smaller area in order to limit these AEs. Adherence was assessed using patient diaries, and the amount of study drug remaining at end of study was also measured by weighing the remaining sample. This latter, more objective measure of adherence suggested that patients in the 5-FU/SA group did indeed apply less drug than those assigned to the placebo group, suggesting that topical AEs of the drug may have had an impact on the way patients applied the drug. Additionally, there were 33 patients with missing adherence data, and the manufacturer did not report the breakdown of this missing data between groups. This missing adherence data further complicates any conclusions that can be drawn about how patients applied drug in the study.

The manufacturer-identified study populations for efficacy analyses did not appear to include an intention-to-treat (ITT) analysis set; rather efficacy analyses were performed on the FAS. To be included in the FAS, patients had to have a baseline evaluation and been treated for at least 12 days, and therefore not all patients were included in the FAS (95% of 5-FU/SA patients and 98% of placebo patients were included in the FAS). In an ITT analysis, all patients would have been included in the analysis, regardless of time on therapy, and the ITT population is considered the most appropriate for analysis of efficacy.

There was a lack of detail in description and reporting of the statistical analyses performed in the included study. This lack of clarity made it challenging to determine how outcomes were being tested and therefore made it difficult to assess the significance of the results.

3.5.2 External validity

Study 0702 included patients with AK on their face/forehead or bald scalp, but did not appear to include patients with AK on the backs of their hands. According to the clinical expert on this review, the backs of the hands are another site of cosmetic concern for patients, particularly those who work with the public. Given the population enrolled in Study 0702, it is questionable whether the results can be generalized to patients with AK on the backs of their hands, and thus this is an important limitation of this study.

There is no data comparing 5-FU/SA with any of the active pharmacological comparators approved for AK in Canada. The active comparator in Study 0702, diclofenac gel, is not approved for use in AK in this country, and is not widely used according to the clinical expert. Therefore the efficacy and harms of 5-FU/SA versus other drugs for AK used in Canada is unknown.

Study 0702 was a multi-centre study, however it was entirely carried out in one country, Germany, and this might potentially pose some generalizability issues. Although the ethnic background (100% Caucasian) of patients in Study 0702 is unlikely to be a generalizability issue according to the clinical expert, treatment practices may vary between Europe and Canada, and therefore patients here may have had a different prior experience with their management of AK versus patients in Germany, potentially being an impact on their response to therapy or their perception of the success of their therapy.

Quality of life does not appear to have been assessed using a validated scale. The manufacturer uses several instruments to rate patient satisfaction with treatment, reported as patient assessment of efficacy, but these appear to simply use basic global descriptors such as “good” or “very good” to rate satisfaction. Therefore, although statistical significance of the differences between groups can be calculated (albeit with the limitations due to lack of accounted for multiple comparisons noted above), the clinical significance of these differences cannot be ascertained. Patient assessment of tolerability was reported in a similar manner, using categories, and we reported this data under patient satisfaction in the review. However, it should be noted that tolerability was also reported under withdrawals due to adverse events and adverse events; thus, some double counting likely occurred.

The included trial was not designed to assess progression to SCC as an efficacy outcome, despite the fact that this is a key complication of AK. The rate of progression from an AK lesion to SCC varies widely, and a definitive estimate of risk is unknown.[4,14] A larger trial of much longer follow up would be needed in order to assess any impact that 5-FU/SA treatment might have on the risk of progression to SCC. Because AK lesions are constantly appearing and patients are relied on to self-administer 5-FU/SA, there is a risk that patients will miss SCC lesions, or miss AK lesions that may eventually progress to SCC, according to the clinical expert.

The manufacturer of 5FU/SA claims that their product would be expected to be more effective than other topical drugs for hyperkeratotic lesions; however, the population in the included study had a mixture of hyperkeratotic and non-hyperkeratotic AK lesions (approximately two-thirds and one-thirds, respectively, of the study population) and no subgroup analyses were performed by the manufacturer. Therefore the efficacy and safety of 5FU/SA in this subpopulation is unknown.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See *0 for detailed efficacy data.*

3.6.1 Complete histological clearance of target lesion

Complete histological clearance of AK in a pre-defined target lesion at eight weeks post-treatment was the primary outcome of the study. Complete clearance of AK was achieved in 70% of patients treated with 5-FU/SA versus 43% of patients treated with placebo, and therefore 5-FU/SA was statistically superior to placebo for the primary outcome (97.5% CI for the difference between groups: [0.13 to 0.40], $P = 0.00019$) (Table 7).

3.6.2 Partial clearance of AK lesions

Clinical response was assessed as a secondary outcome, and the proportion of patients with partial response was 42% with 5FU/SA and 67% with placebo. There was a higher proportion of 5-FU/SA patients with a complete response at eight weeks post-treatment compared with placebo (55% versus 15% of patients) and this difference between groups was statistically significant ($P = 0.00000$) (Table 7).

3.6.3 Reduction in number of AK lesions

There were a larger proportion of lesions cleared in the 5-FU/SA group compared with placebo (50% versus 33% of lesions cleared) and this difference was statistically significant ($P < 0.05$) (Table 7).

3.6.4 Health-related quality of life

This outcome was not investigated.

3.6.5 Other efficacy outcomes

Recurrence of target lesions was assessed at both six months and 12 months of follow up. Of the 742 cleared lesions in the 5-FU/SA group, 8% had recurrence, while of the 189 lesions cleared in the placebo group, 14% recurred. This difference in recurrence rate between groups was statistically significant (Wilcoxon test, $P = 0.02347$). At 12 months follow up, 14% of lesions in the 5-FU/SA group had recurred while 20% of lesions in the placebo group had recurred, and this difference was statistically significant ($P = 0.04419$) (Table 9).

Patients assessment of clinical improvement was a secondary outcome, and a larger proportion of patients treated with 5-FU/SA rated their outcome as “very good” or “good” (83% versus 72% of patients) when compared with placebo, and this difference was statistically significant ($P < 0.00001$). Patients also assessed tolerability, and burning and inflammation appeared to be the most common tolerability issues with 5FU/SA use (Table 9).

TABLE 7: KEY EFFICACY OUTCOMES

	Study 0702		
	5FU/SA N=187	**PLACEBO N=98**	**Statistical analyses 5-FU/SA versus placebo**
Complete Clinical Clearance (Primary End Point)			
Patients at week 20, N (%)			
No AK in target lesion	124 (70)	41 (43)	
AK still present	50 (28)	51 (53)	
Missing result	3 (2)	4 (4)	
Difference between groups [97.5% CI]			*0.27*[a] *[0.13 to 0.40]* *P = 0.000019*
Number of lesions cleared			
Mean (SD) lesions per patient, baseline	5.8 (NR)	5.5 (NR)	
Mean (SD) lesions per patient, end treatment (week 12)	2.8 (NR)	3.7 (NR)	*P = 0.00062*[b] *(one-sided)*
Mean (SD) lesions per patient, post-treatment (week 20)	1.4 (NR)	3.5 (NR)	
Proportion of lesions cleared overall, week 12, n (%)	507/1014 (50)	177/532 (33)	*P* < 0.05
Response – Post Treatment (Week 20)			
Progressive disease	0	1 (1)	*P < 0.00001*[c] *(one-sided)*
Stable disease	4 (2)	16 (17)	
Partial response	74 (42)	62 (67)	
Complete response	97 (55)	14 (15)	

AK = actinic keratosis; FU = fluorouracil; SA = salicylic acid.
Complete response = patients with all lesions cleared.
Source: CSR for Study 0702.[13]
[a] Point estimate calculated by CDR.
[b] Wilcoxon: Z-value.
[c] Cochran-Armitage Trend Test – Full analysis set (comparison of complete responders versus non-complete responders).

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). *See 0 for detailed harms data.*

3.7.1 Adverse events

Of the patients, 95% of those treated with 5FU/SA and 85% of patients of those treated with placebo experienced an adverse event (Table 8). The most common AEs were local skin reactions such as inflammation (73% in 5FU/SA versus 36% placebo), irritation (86% versus 61%) and pruritis (45% versus 41%). Of these, when focusing on just the AE that were classified as severe, the numerical differences between groups is larger, for inflammation (16% in 5FU/SA versus 1% placebo), irritation (21% versus 3%), pruritus (7% versus 0%).

3.7.2 Serious adverse events

SAEs occurred in only 1% of 5-FU/SA patients and 4% of patients treated with placebo (Table 8). There was no single SAE that occurred in more than one patient.

3.7.3 Withdrawals due to adverse events

Withdrawals due to AE occurred in 4% of patients treated with 5-FU/SA and 3% of patients in the placebo group (Table 8). The most common reason for withdrawal due to AE with 5-FU/SA was "application site disorder."

3.7.4 Mortality

There were no deaths in either of the 5-FU/SA or placebo groups.

3.7.5 Notable harms

Notable harms of interest for this review included application site scarring and pigment changes; however, none these events reported in in either the 5-FU/SA groups or placebo (Table 8).

TABLE 8: HARMS (SAFETY SET)

	Study 0702	
	5-FU/SA N = 187	**PLACEBO N = 98**
AEs		
Patients with > 0 AEs, N (%)	178 (95)	83 (85)
Most common AEs (application site, drug-related)		
Inflammation	137 (73)	35 (36)
– *severe*	29 (16)	1 (1)
Irritation (burning)	161 (86)	60 (61)
– *severe*	40 (21)	3 (3)
Pruritis	84 (45)	40 (41)
– *severe*	13 (7)	0
Pain	47 (25)	8 (8)
– *severe*	8 (4)	1 (1)
SAEs		
Patients with > 0 SAEs, N (%)	2 (1)	4 (4)
Most common SAEs	None in > 1 patient	
WDAEs		
WDAEs, N (%)	7 (4)	3 (3)
Most common reasons		
Application site disorders	5	1
Deaths		
Number of deaths, N (%)	0	0
Notable harms		
Most common reasons		
Application site scarring	0	0
Pigment changes	NR	NR

AE = adverse event; 5-FU = fluorouracil; NR = not reported; SA = salicylic acid; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: CSR for Study 0702.[13]

4. DISCUSSION

4.1 Summary of Available Evidence

One pivotal multi-centre DB RCT, Study 0702, met the inclusion criteria for this review. Study 0702 was designed to test the non-inferiority of 5-FU/SA to diclofenac gel and its superiority to placebo in patients with hyperkeratotic (grade I/II) AK. A total of 470 patients were randomized 2:2:1 to 5-FU/SA, diclofenac gel, or placebo. For the purpose of this report, only comparisons between 5-FU/SA and placebo were reviewed, as diclofenac gel is not an approved therapy for AK in Canada. Patients self-applied study drug daily to target areas until lesions had cleared or a maximum of 12 weeks, and assessments were carried out at end of treatment and eight weeks post-treatment. The target areas were the face/forehead (A) and bald scalp (B), and the overall treatment area contained at least four and no more than 10 distinct AK lesions, with a distance of at least one centimetre between lesions, and a maximum lesion diameter of 1.5 cm.[2] The primary outcome of the study was the proportion of patients with complete histological clearance of their pre-defined AK target lesion, at eight weeks post-treatment. Secondary outcomes included assessments of changes from baseline in lesion count, lesion area, lesion response (complete/partial/stable/progressive), as well as physician and patient assessments of efficacy and tolerability.

4.2 Interpretation of Results

4.2.1 Efficacy

The combination of 5-FU/SA elicited a statistically significantly higher proportion of patients achieving complete histological and clinical clearance of their AK lesions, when compared with placebo. Interpretation of these results is challenging, given the large proportion of responders in the placebo group and the lack of an active comparator approved in Canada. The lack of quality of life data are also a limitation of this review, and patient input to CDR clearly indicate the importance of quality of life in this condition. Patients treated with 5-FU/SA did report being satisfied with the progress of their therapy; however, large proportions of patients were satisfied with their results on placebo as well.

According to the manufacturer, the addition of salicylic acid to 5-FU, a topical therapy that is already approved for AK in Canada, is expected to enhance the efficacy of the combination in patients with hyperkeratotic lesions.[12] Salicylic acid is a keratolytic, and therefore it is plausible, as the manufacturer asserts, that it would improve the penetration of 5-FU. This is presumably the reason why the 0.5% concentration of 5-FU in this topical combination with SA is lower than the concentration of 5-FU alone (5%) approved for use in Canada. Whether this combination of 5-FU/SA will be more efficacious in patients with hyperkeratotic AK remains an unanswered question, as subgroup data analyzing responses in this population was not performed in the pivotal study, according to the manufacturer.[15]

Cryotherapy is one of the comparators that the manufacturer focuses on in their Executive Summary to this submission. They note that limitations of cryotherapy include a lack of standardized procedure for its application, and that risks include scarring and hypo/hyperpigmentation.[12] They also assert that cryotherapy is less effective for treating hyperkeratotic lesions. However, as noted above, there are no data from the pivotal trial or any phase III trials that compare 5-FU/SA directly with cryotherapy. The only comparison of these two interventions is from a small (66 participants randomized across two groups) phase II open label RCT (for complete results of this study, see Appendix 6). This study, Simon et al., found no statistically significant difference between 5-FU and cryotherapy, with AK histological clearance achieved in 62% of 5-FU/SA patients and 42% of patients treated with cryotherapy at follow up day 98.[16,17] Other markers of AK lesion response had similar results, no statistically significant

differences between groups, and patients assessment of treatment response was similar between groups. There were numerically more AEs with 5-FU/SA (39% versus 24% of patients with an AE), and application-related events were generally more common with 5-FU/SA. In this study, specific changes in skin quality were also assessed, such as scarring an pigment changes, and scarring appeared to be less common with 5-FU/SA than with cryotherapy (3% versus 16% of patients with mild scarring); however pigment changes were similar in risk between groups (30% versus 25% of patients, respectively). Given the lack of statistically significant difference between treatments and potential limitations (lack of blinding as one example), there is limited evidence to support the manufacturer's assertions about the relative efficacy and safety of 5-FU/SA versus cryotherapy. Furthermore, it is not clear that physicians will choose one option over the other; they may in fact use some combination of both options.

4.2.2 Harms

The most common AEs reported in the included study were similar to what one would expect for a topical combination of 5-FU/SA, namely irritation and inflammation. There is some indication that these adverse effects may have represented tolerability issues for some patients as there were numerically more 5-FU/SA–treated patients who withdrew from the study due to application site issues. There is no indication that the harms associated with the combination of 5-FU/SA lead to SAEs however, and there is no evidence at present that treatment leads to scarring or pigment changes.

4.3 Potential Place in Therapy[1]

Currently available standard treatments for AK include cryotherapy and topical drugs (5-FU, imiquimod, and ingenol mebutate; the latter may be used to treat individual lesions or for treating a wide area [i.e., field therapy]).[1] 5-FU/SA is an addition to currently available topical drugs for the treatment of individual clinical grade I/II (slightly palpable and moderately palpable) lesions. The manufacturer claims that the combination of 5-FU/SA is more effective for hyperkeratotic lesions, but evidence for an advantage of 5-FU/SA as compared with the other topical drugs in this population is lacking.

For individual AK lesions, patients have a choice of physician- administered cryotherapy or self-administered topical therapy. Topical therapy — including 5-FU/SA — is not indicated for grade III lesions, but patients and general practitioners may be not be able to distinguish a grade III lesion from a grade II lesion. The grading of AK lesions (grade I, II, or III) is based on the degree of hyperkeratosis (thickening) and, according to the clinical expert consulted for this review, is highly subjective. It is a concern to rely on patients to self-treat AK lesions. There is a potential harm of patient and general practitioners misdiagnosing an SCC as a hyperkeratotic AK.

Cryotherapy is widely available through dermatologists and general practitioners. The complete response rate is around 80% in most studies.[1] The clinical expert consulted by CDR indicated that when properly applied, the risk of AEs with cryotherapy is minimal. For individual AK lesions, especially the hyperkeratotic lesions, cryotherapy generally works very well and the physician can monitor response to treatment. Lesions that do not respond to treatment need to be reassessed and biopsied to rule out SCC.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

As current treatments can be used to treat grade I and II AK lesions, it is unclear what the place in therapy is for 5-FU/SA. Therefore, the clinical expert consulted by CDR stated that 5-FU/SA would not fulfill any unmet need in therapy.

5. CONCLUSIONS

One DB RCT that was designed to compare 5-FU/SA with placebo and diclofenac gel met the inclusion criteria for this review. The primary outcome of Study 0702 was the proportion of patients with complete clearance of a single pre-defined target AK lesion eight weeks after end of treatment, and 5-FU/SA was statistically significantly superior to placebo for this end point. Other end points related to AK clearance, including the number of lesions cleared, were also statistically significantly improved for 5-FU/SA versus placebo. Quality of life was not assessed; therefore no conclusions can be drawn regarding the effects of 5-FU/SA on quality of life. Surveys found that the majority of patients rate clinical improvement with their therapy as “good” or “very good,” and this was statistically significant versus placebo, although no adjustment was made for multiple comparisons, and the clinical significance of this difference versus placebo is uncertain. There were no consistent reports of specific SAEs noted with use of 5-FU/SA after 12 weeks of treatment, and tolerability issues were predictable AEs of this topical combination: inflammation, erythema, and irritation.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

No input was provided by patient groups. CADTH staff requested and received permission from the Canadian Skin Patient Alliance and the Save Your Skin Foundation to use patient group input they submitted jointly for a previous CDR review for the same indication. The Save Your Skin Foundation provided CDR with one additional survey response from an individual with actinic keratosis (AK).

The Canadian Skin Patient Alliance is a non-profit patient-centred organization serving patient needs to enhance care, promote skin health, and find cures for Canadian skin patients by providing education, information, and a supportive online community and by acting as an umbrella organization for affiliated skin-disease-specific organizations including the Save Your Skin Foundation. The Canadian Skin Patient Alliance has received unrestricted grants from LEO Pharma, Amgen, AbbVie, Galderma, GlaxoSmithKline, Merck, Novartis, Triton, and Valeant Canada.

The Save Your Skin Foundation is a patient-led non-profit organization dedicated to raising awareness of melanoma and non-melanoma skin cancers (NMSCs), which provides patients with access to information about treatment options as well as emotional and financial support to patients and caregivers. The Save Your Skin Foundation has received unrestricted grants from LEO Pharma, Merck, Roche, and Bristol-Myers Squibb.

2. Condition and Current Therapy Related Information

Information was gathered by conducting interviews with six patients who had used ingenol mebutate (from the original submission in 2013) for AK and from a survey for this submission (in which only one person responded) to determine treatment satisfaction, effectiveness, ease of use, side effects, and impact on day-to-day living. Additionally, an online survey was used to collect patient experiences with AK and AK treatments. Six people responded to the 2013 survey and their experiences echoed those of the interviewed patients. One patient responded to the 2016 survey.

AK is a potentially pre-cancerous skin condition usually caused by cumulative sun exposure. It occurs most commonly among those older than 65 and its prevalence is increasing as the Canadian population ages. AK shows up as lesions, rough scaly patches, discoloured areas (pink, red, or brown patches), or wart-like bumps on the skin. In addition, these patches can feel itchy and burn. Patients can often feel embarrassment, anxious, and have lowered self-confidence due to the appearance of the AK lesions. If untreated, AK can progress to NMSC, which can have a profound impact on the individual, including dealing with treatments, cancer-related stress and anxiety, general comorbidities, and the potential for it to spread; some NMSCs can lead to death. There is no way to predict which AK lesions will progress to NMSC.

Current treatment options include cryogenic treatments, topical medications/creams, curettage, electrodessication, and surgery. There are some major concerns with these current treatments, including the inability to finish treatment cycles due to extreme side effects, the negative impact of side effects on quality of life during treatment, the length of treatment (up to 12 weeks), severe discomfort, and the lack of effectiveness. The reaction to treatment can cause anxiety and stress for some patients.

"When I need to have it burned off, the site blisters and looks horrible, weeping, etc. Yuk. I have been told that if it recurs again, I will need surgery, and they will take skin from my cheek up to my nose to accomplish this…very ugly!"

Five patients who had used treatments other than ingenol mebutate were interviewed. These patients all said they experienced discomfort or suffering caused by the treatment. Side effects with treatments like fluorouracil (FU) and imiquimod include skin irritation, burning, redness, dryness, pain, swelling, tenderness, blistering, and changes in skin colour. One patient was unable to complete treatment as his lip hurt so much he was unable to eat. In addition, he compared the side effects to what it must be like to have leprosy and that he took time off work to avoid showing his face in public. Others complain of extreme pain and bleeding sores with treatment. Patients find that completing a 12-week course of imiquimod difficult to cope with as the discomfort increases as treatment progresses. In terms of effectiveness, many patients found that even if they were able to complete a treatment course, they did not experience a complete resolution of their AK lesions.

While many AK patients are self-sufficient and need minimal help from caregivers, those who are elderly may need a caregiver to apply their treatment, which can be distressing when the patient is already suffering from inflamed and painful skin. Additionally, patients may stay home from work or stop participating in social and recreational activities, which can impact the entire family.

3. Related Information About the Drug Being Reviewed

AK is not generally perceived as being as serious as other NMSCs and many patients are reluctant to complete the currently available long and debilitating treatment courses to reduce their risk of cancer. A shorter treatment with reduced trauma to the skin is more desirable to the growing population of patients diagnosed with AK. Patients are hoping that they will be able to avoid more time off work, stay more productive, use fewer pain medications, and experience considerably less stress with the use of any newly available medication.

None of the responding patients have had experience with Actikerall.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 27, 2016
Alerts:	Weekly search updates until February 15, 2017
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
ppez	Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY
1. keratosis, actinic/
2. Keratos*.ti,ab.
3. 1 or 2
4. (5-fluorourac* or 5fluorourac* or fluorourac* or 5fu* or 5-fu*).ti,ab,ot,kf,hw,rn,nm.
5. (actikeral* or LAS-41005 or LAS41005).ti,ab,kf,ot,hw,rn,nm.
6. 4 or 5
7. 3 and 6
8. 7 use ppez
9. *actinic keratosis/
10. keratos*.ti,ab.
11. (5-fluorourac* or 5fluorourac* or fluorourac* or 5fu* or 5-fu*).ti,ab,ot,kw.
12. (actikeral* or LAS-41005 or LAS41005).ti,ab,ot,kw.
13. 11 or 12
14. 9 or 10
15. 13 and 14
16. 15 use oemezd
17. 8 or 16
18. remove duplicates from 17
19. conference abstract.pt.
20. 18 not 19

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	September 2016
Keywords:	Actikerall and keratosis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Kumar S, Kumar R, Medhi B, Sinha VR. Novel strategies for effective actinic keratosis treatment: A review Topical fluorouracil (5-FU) for premalignant keratoses. Current Cancer Therapy Reviews. 2015;11(2):119-32.	Review
Herranz P, Morton C, Dirschka T, Azeredo RR, Roldán-Marin R. Low-Dose 0.5% 5-Fluorouracil/10% salicylic acid topical solution in the treatment of actinic keratoses. J Cutan Med Surg. 2016 Jul 21.	
Nguyen HP, Rivers JK. Actikerall (5-Fluorouracil 0.5% and Salicylic Acid 10%) topical solution for patient-directed treatment of actinic keratoses. Skin Therapy Lett. 2016 May;21(3):1-3.	
Rhavar M, Lamel SA, Maibach HI. Randomized, vehicle-controlled trials of topical 5-fluorouracil therapy for actinic keratosis treatment: an overview. Immunotherapy. 2012;4(9):939-45.	Systematic review
Stockfleth E, Sibbring GC, Alarcon I. New topical treatment options for actinic keratosis: a systematic review. Acta Derm Venereol. 2016 Jan;96(1):17-22.	
Werner RN, Jacobs A, Rosumeck S, Erdmann R, Sporbeck B, Nast A. Methods and results report - evidence and consensus-based (S3) guidelines for the treatment of actinic keratosis -International League of Dermatological Societies in cooperation with the European Dermatology Forum. J Eur Acad Dermatol Venereol. 2015 Nov;29(11):e1-66.	Guidelines
Simon JC, Dominicus R, Karl L, Rodriguez R, Willers C, Dirschka T. A prospective randomized exploratory study comparing the efficacy of once-daily topical 0.5% 5-fluorouracil in combination with 10.0% salicylic acid (5-FU/SA) vs. cryosurgery for the treatment of hyperkeratotic actinic keratosis. J Eur Acad Dermatol Venereol. 2015 May;29(5):881-9.	Phase II

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 9: OTHER EFFICACY OUTCOMES

	Study 0702		
	5-FU/SA N = 187	**PLACEBO N = 98**	**Statistical Analyses**
Patient assessment of clinical improvement (post-treatment follow up, week 20)			
Rating of "good" or "very good," n (%)	146 (83)	67 (72)	
P value			*P* < 0.00001
Patient assessment of tolerability (end of treatment, week 12)			
Patients reporting:			Cochran-Armitage Trend Test — FAS
Burning	66 (38)	57 (61)	*P* = 0.00001
• None			
• Little	60 (34)	27 (29)	
• Moderate	30 (17)	7 (8)	
• Strong	13 (7)	2 (2)	
• Very strong	6 (3)	0	
Inflammation	86 (49)	72 (77)	*P* < 0.00001
• None			
• Little	39 (22)	14 (15)	
• Moderate	36 (21)	6 (7)	
• Strong	11 (6)	1 (1)	
• Very strong	3 (2)	0	
Itching	124 (71)	67 (72)	*P* = 0.17008
• None			
• Little	32 (18)	21 (23)	
• Moderate	17 (10)	5 (5)	
• Strong	1 (1)	0	
• Very strong	1 (1)	0	
Pain	159 (91)	89 (96)	*P* = 0.03270
• None			
• Little	6 (3)	3 (3)	
• Moderate	5 (3)	1 (1)	
• Strong	4 (2)	0	
• Very strong	1 (1)	0	
Recurrence of target lesions previously cleared			
Recurrent lesions at 6 months, n (%)	62/742 (8)	26/189 (14)	*P* = 0.02347
At 12 months, n (%)	103/725 (14)	37/183 (20)	*P* = 0.04419
P value		NR	Wilcoxon Test — FAS

AK = actinic keratosis; DICLO = diclofenac; 5-FU = fluorouracil; SA = salicylic acid.
Source: CSR for Study 0702.[13]
Complete response = all lesions cleared.

APPENDIX 5: SUMMARY OF OTHER STUDIES

Simon et al. was an open-label RCT (n = 66 randomized 1:1 across two groups) centered in Germany that compared 5-FU/SA with cryotherapy in patients with AK grade II/III. There were also patients with grade I AK at baseline (9% with 5-FU/SA and 24% with cryotherapy); therefore, these patients are presumably protocol violations.

The lack of blinding and the fact that it was a manufacturer-sponsored study are potential sources of bias. The technique for administration of cryotherapy is key to its success; therefore, if there was investigator bias, this may have had an impact on treatment success with cryotherapy. For example, freezing time can be an important determinant of the success of cryotherapy;[18,19] however, freezing times were left to the discretion of the investigator and were not reported by the manufacturer. The study was not powered to assess superiority of 5-FU/SA to cryotherapy, and there was no statistically significant difference in lesion clearance between 5-FU/SA and cryotherapy, with clearance in 62% versus 42% of patients, respectively. The cryotherapy response in this study was considered to be quite low according to the clinical expert consulted by CDR, a potential generalizability issue. Patients in the study tended to have more severe AK (i.e., a higher proportion of patients with grade III and a lower proportion of patients with grade I) than the study included in the systematic review, and it is possible this population is more difficult to treat with cryotherapy. There were no statistically significant differences between groups for other efficacy outcomes related to lesion clearance, and patient satisfaction results were similar between groups. Regarding harms, 5-FU/SA patients were at numerically higher risk of having an adverse event (AE), with 39% of 5FU/SA patients and 24% of cryotherapy patients with an AE. Patients treated with 5FU/SA were also at numerically higher risk of having an AE related to topical administration such as erythema (82% versus 52% of patients) or burning (68% versus 15% of patients), although pain was numerically less common with 5FU/SA than with cryotherapy (6% versus 30% of patients). Given its small sample size, this study adds little to the understanding of the relative efficacy/safety of 5-FU/SA to cryotherapy; however, it does help generate the hypothesis that the combination of 5-FU/SA may exhibit superior efficacy to cryotherapy, while at the same time being less tolerable than cryotherapy, and this hypothesis need to be tested in a trial of sufficient power to address these questions.

TABLE 10: STUDY DESIGN (PHASE II STUDY)

		Simon et al.
DESIGNS AND POPULATIONS	**Study Design**	OL RCT
	Locations	Germany (4 centres)
	Study period	April 13, 2011 to August 20, 2012
	Randomized (N)	N = 67
	Inclusion Criteria	Female or male patients between 18 and 85 years of age inclusive and suffering from 4 to 10 AK lesions grade II and III (according to Olsen et al., 1991) in their face and forehead or on their bald scalp. The summarized test area of all single AK lesions was not to cover a total area of > 25 cm^2 (including a 5 mm to treat surrounding area).
	Exclusion Criteria	Had received treatment of AK within the treatment area (face / scalp) in the three months preceding this clinical trial. Had known hypersensitivity to 5-FU or SA, acetylsalicylic acid.
DRUGS	**Intervention**	5-FU (0.5%)/SA (10%) applied daily for up to 6 weeks or until complete lesion clearance or ulceration of the treated area. Applied to each target lesion and a surrounding area of approximately 5 mm to treat surrounding subclinical parts of the AK lesions.
	Comparator(s)	One cryotherapy was performed on day 1 of the trial; a further cryotherapy could be performed at 3 weeks after the first cryotherapy, if necessary.
DURATION	**Phase**	
	Run-in	NR
	Double-blind	14 weeks (8 weeks post-treatment follow up)
	Follow up	NR
OUTCOMES	**Primary End Point**	Histological clearance of one pre-defined target lesion at 8 weeks after end of treatment with 5-FU/SA, respectively 14 weeks after first cryotherapy.
	Other End Points	• Lesion response (100% clearance, 75% clearance) • Lesion size • Lesion count • Assessment of tolerability and safety by physician's global assessment scores (PGA, PGT) • Patient's global assessment of efficacy and tolerability • Assessment of cosmetic outcome
NOTES	**Publications**	Simon 2015[17]

AK = actinic keratosis; 5-FU = fluorouracil (0.5%); NR = not reported; OL = open label; PGA = Physician's Global Assessment; PGT = Physician's global tolerability score; RCT = randomized controlled trial; SA = salicylic acid.
Source: CSR.[16]

TABLE 11: BASELINE CHARACTERISTICS (PHASE II STUDY)

Title	5-FU/SA N = 33	CRYOTHERAPY N = 33
Mean age	70.6 (8.3)	71.3 (7.6)
Male, n (%)	29 (88)	29 (88)
Caucasian, n (%)	33 (100)	33 (100)
Mean (SD) lesions per patient	3.4 (3.9)	3.6 (3.6)
Mean (SD) total lesion area per patient, mm^2	5.5 (1.6)	5.4 (1.7)
Location of lesions:		
– bald scalp	15 (46)	12 (36)
– face (forehead)	13 (39)	9 (27)
– bald scalp and face/forehead	5 (15)	12 (36)
Biopsy diagnosis, n (%)		
AK I	3 (9)	8 (24)
AK II	26 (79)	20 (61)
AK III	4 (12)	5 (15)

AK = actinic keratosis; 5-FU = fluorouracil (0.5%), SA = salicylic acid; SD = standard deviation.
Source: CSR.[16]

TABLE 12: DISPOSITION (PHASE II STUDY)

	Simon	
	5-FU/SA	CRYOTHERAPY
Screened, N		
Randomized, N (%)	34	33
Randomized and treated, n (%)	33	33
Discontinued, N (%)	1	1
• **Adverse event**	0	0
• **Lack of tolerability**	0	0
• **Lost to follow up**	0	1
• **Other (e.g., withdrawn consent)**	1	0
FAS, N	33	33
PP, N	26	31
Safety, N	33	33

FAS = full analysis set; 5-FU = fluorouracil (0.5%); PP = per protocol; SA = salicylic acid.
Source: CSR.[16]

TABLE 13: EFFICACY OUTCOMES (PHASE II STUDY)

	Simon		
	5-FU/SA N = 33	**CRYOTHERAPY N = 33**	**Statistical Analysis Difference Between Groups (95% CI)**
Complete Histological Clearance of a Single Target Lesion (Primary End Point)			
Patients at day 98 visit, N (%)			
No AK	18 (62)	13 (42)	
AK still present	11 (38)	18 (58)	
Missing result	4	2	
Difference between groups (95% CI)			20.13 (–4.64 to 44.90)
Reduction in Number of AK Lesions			
Mean (SD) lesions at baseline	8.1 (1.2)	8.0 (1.1)	
Mean (SD) change by day 98	–5.2 (2.9)	–5.7 (2.4)	
LSM difference between groups (95% CI)			–0.606 (–1.855 to 0.644) *P* = 0.336
Proportion of lesions cleared (95% CI)	–64.5 (52.6 to 76.4)	–72.1 (62.3 to 81.9)	
Patient Assessment of Clinical Improvement			
Rating of "good" or "very good" at day 98, n (%)	27 (82)	25 (78)	
P value			NR
Recurrence of Target Lesions Previously Cleared			
Recurrent lesions at 6 months, n (%)	13/172	38/178	
Recurrent lesions in patients at 6 months, n (%)	9 (27)	21 (68)	
Difference between groups (95% CI)			–41.88 (–64.49 to –19.26)
Response — Day 98			
			Difference between groups (95% CI)
Partial clearance	17/33 (52)	20/32 (63)	–11.0% (–34.90 to 12.93)
Complete clearance	11/33 (33)	8/32 (25)	8.33% (–13.66 to 30.33)

AK = actinic keratosis; CI = confidence interval; 5-FU = fluorouracil (0.5%); LSM = least squares mean; SA = salicylic acid; SD = standard deviation.
Source: CSR.[16]
Complete clearance rate: percentage of participants who manifested no clinically visible AK lesions.
Partial clearance rate: percentage of participants with at least 75% reduction in the number of AK lesions

TABLE 14: HARMS (PHASE II STUDY)

	SIMON	
	5-FU/SA N = 33	CRYOTHERAPY N = 33
AEs		
Patients with > 0 AEs, N (%)	13 (39)	8 (24)
Local skin reactions (not included as AEs unless severe)		
• Erythema	27 (82)	17 (52)
• Scabbing/crusting	24 (73)	22 (67)
• Burning	23 (68)	5 (15)
• Pruritis	7 (21)	3 (9)
• Pain	2 (6)	10 (30)
• Maceration	6 (18)	0
SAEs		
Patients with > 0 SAEs, N (%)	1 (3)	0
Most common SAEs	SCC	
WDAEs		
WDAEs, N (%)	3 (9)	0
Most common reasons		
Application site disorders		
Deaths		
Number of deaths, N (%)	0	0
Notable harms (Follow up Day 98)		
Scarring (mild)	1 (3)	5 (16)
Mottled or irregular pigmentation-mild	10 (30)	7 (22)
Mottled or irregular pigmentation-moderate	0	1 (3)

AE = adverse event; 5-FU = fluorouracil (0.5%); SA = salicylic acid; SAE = serious adverse event; SCC = squamous cell carcinoma; WDAE = withdrawal due to adverse event.
Source: CSR.[16]

REFERENCES

1. de Berker D, McGregor JM, Hughes BR. Guidelines for the management of actinic keratoses. Br J Dermatol. 2007;156:222-30.
2. Gupta AK, Paquet M. Ingenol mebutate: a promising treatment for actinic keratoses and nonmelanoma skin cancers. J Cutan Med Surg. 2013 May;17(3):173-9.
3. Dodson JM, DeSpain J, Hewett JE, Clark DP. Malignant potential of actinic keratoses and the controversy over treatment. A patient-oriented perspective. Arch Dermatol. 1991 Jul;127(7):1029-31.
4. Ghuznavi N, Nocera NF, Guajardo AR, Weinberg JM. Emerging medical treatments for actinic keratoses, squamous cell carcinoma and basal cell carcinoma. Clinical Investigation. 2012;2(9):909-21.
5. Stockfleth E, Terhorst D, Braathen L, Cribier B, Cerio R, Ferrandiz C, et al. Guideline on Actinic Keratoses [Internet]. Zurich (CH): European Dermatology Forum; 2010 Oct 20. [cited 2016 Nov 10]. Available from: http://www.ensas.ee/docs/management_of_actinic_keratoses.pdf
6. National Institute for Health and Care Excellence. ESNM14: Actinic keratosis: ingenol mebutate gel [Internet]. London: The Institute; 2013 Mar 19. [cited 2016 Nov 10]. (Evidence summary: new medicine). Available from: https://www.nice.org.uk/guidance/esnm14/resources/actinic-keratosis-ingenol-mebutate-gel-1502680802891461
7. Berman B. New developments in the treatment of actinic keratosis: focus on ingenol mebutate gel. Clin Cosmet Investig Dermatol [Internet]. 2012 [cited 2016 Nov 10];5:111-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3430094/pdf/ccid-5-111.pdf
8. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; 2009 -; 2016 Nov 22 [cited 2016 Nov 22]. Available from: https://www.e-therapeutics.ca Subscription required.
9. Actikerall (.5% fluorouracil and 10% salicylic acid): Topical antineoplastic agent [product monograph]. Mississauga (ON): Cipher Pharmaceuticals Inc.; 2015 Aug 7.
10. Stockfleth E, Kerl H, Zwingers T, Willers C. Low-dose 5-fluorouracil in combination with salicylic acid as a new lesion-directed option to treat topically actinic keratoses: histological and clinical study results. Br J Dermatol. 2011 Nov;165(5):1101-8.
11. Health Canada reviewer's report: Actikerall (5-fluorouracil and salicylic acid) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2014 Jul 29.
12. CDR submission: Actikerall, .5% fluorouracil and 10% salicylic acid. Company: Cipher Pharmaceuticals Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Cipher Pharmaceuticals Inc.; 2016 Sep 16.
13. Clinical Study Report: H 1005 6002-0702. Study on the efficacy of Verrumal compared to placebo and Solaraze in the treatment of actinic keratosis grade I to II [**CONFIDENTIAL** internal manufacturer's report]. London (UK): Focus - Clinical Drug Development GmbH; 2009 Oct 7.
14. Stockfleth E. The paradigm shift in treating actinic keratosis: a comprehensive strategy. J Drugs Dermatol. 2012 Dec;11(12):1462-7.
15. Cipher Pharmaceuticals Inc. response to November 3rd 2016 CDR request for additional information regarding the Actikerall CDR review [**CONFIDENTIAL** additional manufacturer's information]. Mississauga (ON): Cipher Pharmaceuticals Inc.; 2016 Nov 9.

16. Clinical Study Report: H 1005 6002-1007. A prospective comparator controlled randomized exploratory study on the efficacy of LAS 41005 compared to cryotherapy in subjects with hyperkeratotic actinic keratosis [**CONFIDENTIAL** internal manufacturer's report]. London (UK): Focus - Clinical Drug Development GmbH; 2013 Jan 15.

17. Simon JC, Dominicus R, Karl L, Rodriguez R, Willers C, Dirschka T. A prospective randomized exploratory study comparing the efficacy of once-daily topical 0.5% 5-fluorouracil in combination with 10.0% salicylic acid (5-FU/SA) vs. cryosurgery for the treatment of hyperkeratotic actinic keratosis. J Eur Acad Dermatol Venereol. 2015 May;29(5):881-9.

18. Thai KE, Fergin P, Freeman M, Vinciullo C, Francis D, Spelman L, et al. A prospective study of the use of cryosurgery for the treatment of actinic keratoses. Int J Dermatol. 2004 Sep;43(9):687-92.

19. de Berker D, McGregor JM, Mohd Mustapa MF, Exton LS, Hughes BR. British Association of Dermatologists guidelines for the care of patients with actinic keratosis 2016. London: British Association of Dermatologists; 2016.