Fluorouracil Cream 0.5% for Actinic Keratoses on Multiple Body Sites: An 18-Month Open-Label Study

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This prospective 18-month, open-label, multicenter study assessed the long-term safety and efficacy of fluorouracil cream 0.5% in 277 participants with multiple actinic keratoses (AKs) on the face/anterior scalp and other body sites. Two treatment/observation cycles were separated by 12 months. During treatment cycle 1 (TC1), all participants were treated with fluorouracil cream 0.5% for 4 weeks with 4-week follow-up. Twelve months later, all participants were assessed for treatment cycle 2 (TC2); participants with face/anterior scalp AKs (N=98) were re-treated with fluorouracil cream 0.5% for 4 weeks with 4-week follow-up. Only 4 participants (1.4%) experienced a treatment-related adverse event (AE) that was not an application site reaction or eye irritation. No unexpected AEs were reported; most were mild or moderate. After TC1 (week 8), the number of AK lesions was significantly reduced on the face/anterior scalp and all other treated body sites (P<.0001). Clearance rates were 30.5% (hands), 39.8% (face/anterior scalp), and 79.1% (lips). After TC2 (week 60), face/anterior scalp AKs were significantly reduced (P<.0001) and the clearance rate was 33.3%. This study indicates that fluorouracil cream 0.5% with a patented microsponge delivery system was well-tolerated and effective in treating and preventing recurrence of AK lesions up to 18 months after initial treatment.

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Actinic keratosis (AK) is a premalignant condition characterized by atypical keratinocytes with features common to squamous cell carcinoma (SCC).[1-4] Common dysplastic epidermal lesions were identified during 47 million patient visits from 1990 to 1999.[5] The estimated rate of evolution of AK to SCC is approximately 10%. Potentially malignant AK lesions are indistinguishable from other AK lesions; therefore, treatment of AK lesions often is advocated to prevent their progression to SCC.[6-8]

Topical fluorouracil is considered a useful therapy for patients with extensive widespread AK lesions because it has the potential to treat subclinical lesions that may be present in patients with notable sun damage.[9,10] Because of the potential toxicity of fluorouracil, a more ideal topical formulation would allow a substantial amount of drug to remain in the skin at the site of action with minimal systemic exposure. One formulation—fluorouracil cream 0.5%—delivers a lower concentration of

fluorouracil to the affected skin using a patented microsponge system, resulting in lower systemic absorption and higher retention of fluorouracil in the skin.[11]

The objective of the following study was to assess the safety and efficacy of fluorouracil cream 0.5% in the treatment of AK lesions on the face, including the anterior scalp, and other body sites.

Methods

Design and Objectives—This 18-month, phase 4, open-label study, conducted at 25 outpatient centers in the United States, consisted of 2 treatment/observation cycles and a final study visit.[12] The primary objective of the study was to assess the safety of fluorouracil cream 0.5% in the treatment of AK lesions on the face, including the anterior scalp (if applicable), and other body sites (ie, lips, ears, neck, arms, hands, and/or posterior scalp) after 4 weeks of treatment. Secondary objectives included assessment of the reduction in the number and clearance of lesions on the face and other body sites; determination of the recurrence rate of facial lesions; and identification of the need for retreatment of facial lesions 12 months after initial treatment.

Treatment Cycle 1—At the baseline visit for treatment cycle 1 (TC1), an AK lesion count by body site was performed and recorded. Participants were provided with tubes of fluorouracil cream 0.5% and instructions for once-daily application. The first application of study medication to the designated treatment area (as determined by the investigator) was supervised by study center personnel. If the study medication was discontinued because of intolerability at 1 designated body site, the participant was allowed to continue treatment to other designated body sites for up to 4 weeks, as tolerated.

Participants returned after 4 weeks of treatment, at which time they were observed and questioned regarding adverse events (AEs). Treatment compliance was monitored and hydrocortisone cream 2.5% was provided (if needed) for intolerable skin irritation.

At the 4-week follow-up visit (week 8), an AK lesion count was performed. Adverse events were recorded, and any residual lesions were removed with cryotherapy. Participants undergoing cryotherapy returned for a posttreatment follow-up visit at week 12. Residual lesions were counted and then treated with cryotherapy, and any persistent suspicious lesions were biopsied. Adverse events also were noted.

Treatment Cycle 2—Participants returned to the study center 12 months (52 weeks) after their first application of study medication to begin treatment cycle 2 (TC2). Participants with no face/anterior scalp lesions were instructed to return in 6 months (week 78) for the final study visit. Participants with residual lesions on previously treated areas other than the face/anterior scalp were treated with cryotherapy and were instructed to return in 6 months (week 78) for the final study visit.

At this visit (week 52), an AK lesion count only on the face and anterior scalp was recorded. Participants with residual lesions were instructed to apply study medication once daily for the next 4 weeks, as tolerated. These participants returned for an end-of-treatment visit (week 56), at which time compliance was assessed and AEs were recorded. Participants returned for a follow-up visit at week 60 when face/anterior scalp lesion counts were recorded and any residual lesions were treated with cryotherapy. Participants undergoing cryotherapy returned at week 64. Any treated lesions were examined, suspicious or persistent lesions were biopsied, and participants were questioned regarding any AEs or changes in the use of concomitant medications.

Final Visit Assessment (Week 78)—All participants returned for the final study visit 18 months after their first treatment with fluorouracil cream 0.5%. A final count of lesions on the face and/or anterior scalp was performed, any persistent suspicious lesions were biopsied, and participants were questioned regarding AEs.

Safety Assessments—Safety, the primary objective of the study, was assessed by summarizing the AE incidence, severity, and relationship to study medication, including all application site reactions and eye irritation. These assessments were performed by the same investigator during each treatment cycle and more than 30 days after the last study treatment cycle.

Efficacy Assessments—The primary efficacy assessments during TC1 included reduction and clearance rates of AK lesions of the face/anterior scalp, lips, ears, neck, arms, hands, or posterior scalp at week 8. During TC2, only reduction and clearance rates of AK lesions of the face/anterior scalp were assessed. The number and percentage of participants achieving complete elimination of all AK lesions also were determined. The same investigator counted AK lesions during each evaluation.

Statistical Analyses—This study was powered to observe 1 or more AEs in 1.2% of participants (probability of 95%). All safety and efficacy analyses were conducted on the intention-to-treat population (ie, participants who received at least 1 treatment with fluorouracil cream 0.5%). Changes from baseline in AK lesions were analyzed using a paired *t* test. For efficacy analyses, statistical tests were carried out at $\alpha = .05$.

Results

Participant Characteristics and Disposition—A total of 277 individuals were screened for this study and all were enrolled. All participants were white with a mean age of 67.4 years (range, 36–92 years). The majority of participants were men (81.2%) with fair skin (73.6%). At baseline, 24.2% of participants reported a history of irritation of the face. Irritation of the face at study entry was ongoing in approximately 97% of these participants. The mean number of all AK lesions was 39.8. The most common locations of lesions included the face/anterior scalp and arms (Table 1).

All 277 participants received at least 1 application of study medication during TC1; 203 (73.3%) completed treatment in all designated areas. A total of 98 participants were treated in TC2 and received at least 1 application of study medication; 88 (89.8%) completed treatment in all designated treatment areas. Fifty-two (18.8%) of the original participants did not complete the study; the majority either withdrew consent (n=29; 10.5%) or were lost to follow-up (n=12; 4.3%).

A total of 229 (82.7%) participants were determined to be compliant in TC1, which was defined as applying 80% or more of protocol-specified doses. Of the 98 participants with face/anterior scalp AK lesions treated in TC2, 91 (92.9%) were compliant with the protocol-scheduled treatment.

A total of 269 (97.1%) participants used concomitant medications during the study; 177 (63.9%) used a topical corticosteroid, primarily hydrocortisone.

Safety and Tolerability—One participant discontinued due to a treatment-related AE in TC1 (moderate conjunctivitis during week 2). No participants discontinued because of an AE during or after TC2.

Almost all treatment-related AEs involved either the skin and appendages or the eyes (Table 2). Although the application site reactions of skin and appendages were rated as severe in 53 (19.1%) participants and eye irritation was judged as severe in 3 (1.1%) participants during TC1, only 1 participant discontinued from the study due to a treatment-related AE (ie, moderate conjunctivitis).

During both posttreatment periods, no treatment-related AEs were experienced by 2% or more of participants. Six (2.2%) participants experienced a treatment-related AE involving the skin (5 application site reactions; 1 treatment-related skin hypertrophy). No treatment-related AEs involving eye irritation were reported posttreatment.

Two participant deaths were reported during the study: one death due to an unspecified carcinoma and one death due to fatal cardiac arrest, occurring approximately 5 and 6 months after the last application of study medication, respectively. Neither death was considered to be related to study medication.

Efficacy—Interim efficacy results have been reported elsewhere.[12] During TC1, statistically significant reductions were noted in the number of AK lesions from baseline to week 8, regardless of body site ($P<.0001$)(Figure 1). Mean percentage reduction in AK lesions from baseline to week 8 ranged from 56.5% (hands) to 86.0% (face/anterior scalp). Furthermore, a statistically significant decrease (77%) was observed in the total number of AK lesions on all body sites ($P<.0001$). At week 8, clearance rates for AK lesions ranged from 30.5% (hands) to 79.1% (lips)(Figure 2).

During TC2, the mean AK lesion count on the face/anterior scalp decreased by 74.3% from week 52 to week 60 (7.0 to 1.8; $P<.0001$)(Figure 3). Clearance rates of AK lesions on the face/anterior scalp at week 60 (33.3%) were similar to week 8 (39.8%) (Figure 2).

Final visit assessments (week 78) included participants who received retreatment during TC2 as well as participants who did not receive a second cycle of treatment (no face/anterior scalp lesions at the week 52 follow-up visit). At this final visit, an overall decrease was seen from week 8 in the mean number of AK lesions for all designated treatment areas (Figure 1), and the total mean number of AK lesions decreased from 9.7 to 5.1. One exception was the mean number of face/anterior scalp lesions, which increased from 2.2 to 2.7 (Figure 3). Although 54 of 92 participants assessed (58.7%) had recurrence of face/anterior scalp AK lesions at the beginning of TC2 (week 52), the recurrence rate at the final study visit (week 78) decreased to 45.8%.

Comment

The results of this study indicate that fluorouracil cream 0.5% is effective for the long-term treatment of AK lesions on the face/anterior scalp as well as other body sites including the lips, ears, neck, arms, hands, and posterior scalp.

Compliance with topical 5-fluorouracil in patients with AK lesions is a practical consideration given the inflammatory responses associated with treatment.[13] In this study, 83% and 93% of participants were judged to be compliant with the use of fluorouracil cream 0.5% in TC1 and TC2, respectively.

Overall, only 4 participants (1.4%) experienced a treatment-related AE that was not an application site reaction or eye irritation, and no unexpected AEs were reported. These safety results are consistent with and corroborate the results of earlier studies with fluorouracil cream 0.5% for the treatment of AK.[11,14,15]

Table 1.
Baseline Demographic and Clinical Characteristics of the Study Population

	ITT/Safety Population[a] (N=277)
Age, y	
Mean (SD)	67.4 (9.78)
Race, n (%)	
White	277 (100)
Gender, n (%)	
Male	225 (81.2)
Female	52 (18.8)
Complexion, n (%)	
Fair	204 (73.6)
Medium	73 (26.4)
Dark	0 (0)
Baseline Irritation, n (%)	
Eye	39 (14.1)
Face	67 (24.2)
AK Lesion Count[b]	
Total	
Participants with AK lesions, n (%)	277 (100)
Mean (SD)	39.8 (28.1)
Face/anterior scalp	
Participants with AK lesions, n (%)	277 (100)
Mean (SD)	15.7 (11.0)
Lips	
Participants with AK lesions, n (%)	44 (15.9)
Mean (SD)	2.0 (1.3)
Ears	
Participants with AK lesions, n (%)	158 (57.0)
Mean (SD)	4.1 (2.9)
Neck	
Participants with AK lesions, n (%)	88 (31.8)
Mean (SD)	4.8 (4.9)
Arms	
Participants with AK lesions, n (%)	192 (69.3)
Mean (SD)	12.3 (13.7)
Hands	
Participants with AK lesions, n (%)	214 (77.2)
Mean (SD)	9.2 (7.5)
Posterior scalp	
Participants with AK lesions, n (%)	125 (45.1)
Mean (SD)	9.5 (7.9)

Abbreviations: ITT, intention to treat; SD, standard deviation; AK, actinic keratosis.
[a]The ITT/safety population consists of participants who received at least 1 treatment with fluorouracil cream 0.5%.
[b]The number of AK lesions differs according to body site.

Table 2.
Treatment-Related AEs[a]

System Organ Class/ Preferred Term	Treatment Cycle 1 (N=277)		Treatment Cycle 2 (N=98)	
	Total, n (%)	Severe, n (%)	Total, n (%)	Severe, n (%)
Participants with at least 1 AE[b]	245 (88.4)	54 (19.5)	74 (75.5)	10 (10.2)
Skin and appendages	241 (87.0)	53 (19.1)	73 (74.5)	9 (9.2)
Application site reactions	16 (5.8)	3 (1.1)	NA	NA
Arms (erythema)	8 (2.9)	0 (0)	NA	NA
Hand (erythema)	8 (2.9)	2 (0.7)	NA	NA
Face (burning)	10 (3.6)	0 (0)	2 (2.0)	0 (0)
Face (burning, other)	6 (2.2)	0 (0)	3 (3.1)	3 (3.1)
Face (dryness, erythema)	7 (2.5)	1 (0.4)	4 (4.1)	0 (0)
Face (dryness, pain, erythema)	NA	NA	3 (3.1)	1 (1.0)
Face (dryness, pain, other)	NA	NA	2 (2.0)	1 (1.0)
Face (edema, dryness, pain, erythema, burning, pruritus, other)	6 (2.2)	5 (1.8)	NA	NA
Face (erythema)	16 (5.8)	0 (0)	9 (9.2)	0 (0)
Face (erythema, burning)	NA	NA	5 (5.1)	0 (0)
Face (erythema, burning, pruritus, other)	NA	NA	3 (3.1)	0 (0)
Face (erythema, burning, other)	6 (2.2)	1 (0.4)	NA	NA
Face (erythema, other)	7 (2.5)	1 (0.4)	7 (7.1)	1 (1.0)
Face (erythema, pruritus)	6 (2.2)	1 (0.4)	NA	NA
Face (pain, erythema)	7 (2.5)	0 (0)	NA	NA
Face (pain, erythema, other)	6 (2.2)	0 (0)	NA	NA
Face (other)	9 (3.2)	0 (0)	3 (3.1)	0 (0)
Special senses	68 (24.5)	3 (1.1)	13 (13.3)	1 (1.0)
Conjunctivitis: eye (burning)	10 (3.6)	0 (0)	NA	NA
Conjunctivitis: eye (other)	7 (2.5)	0 (0)	3 (3.1)	0 (0)
Conjunctivitis: eye (watering)	21 (7.6)	1 (0.4)	2 (2.0)	0 (0)

Abbreviations: AE, adverse event; NA, not applicable.
[a]Experienced by ≥2% of participants.
[b]Number of participants with at least 1 AE regardless of severity.

The severity of facial irritation with the use of fluorouracil cream 0.5% has been reported to peak near treatment cessation in participants treated for 1 or 2 weeks and to reach a plateau during the third week for patients treated for longer durations.[14,15] In this study, stabilization of irritation was observed with continued treatment, which confirms prior suggestions that increased irritation may not correlate with increased efficacy.[16]

Our study has several limitations that can affect the interpretation of the results. The study was not randomized and did not include a control group. However, this phase 4 study was designed primarily to further evaluate the safety of treatment with fluorouracil cream 0.5% and the rate of recurrence of AK lesions following treatment. Furthermore, efficacy was assessed by AK lesion counts identified by visual inspection without confirmation by skin biopsy, which is standard with other studies of fluorouracil cream 0.5% and other topical AK treatments.

Topical corticosteroid use beginning 30 or more days after the last application of study medication could have influenced the incidence and/or severity of application site reactions in the posttreatment periods but not the incidence/severity of these types of AEs during the treatment and follow-up periods. The use of hydrocortisone in alleviating the potential application site reactions can be an

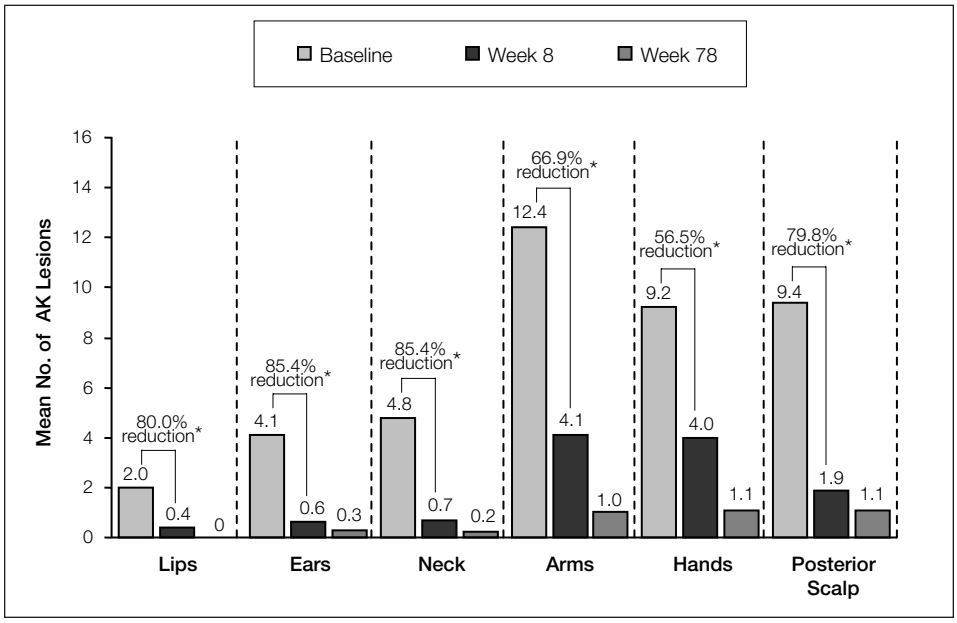

Figure 1. Mean number of actinic keratosis (AK) lesions at baseline, week 8, and week 78 (final study results) for all other treatment areas (intention-to-treat population; N=277). Asterisk indicates *P*<.0001 vs baseline.

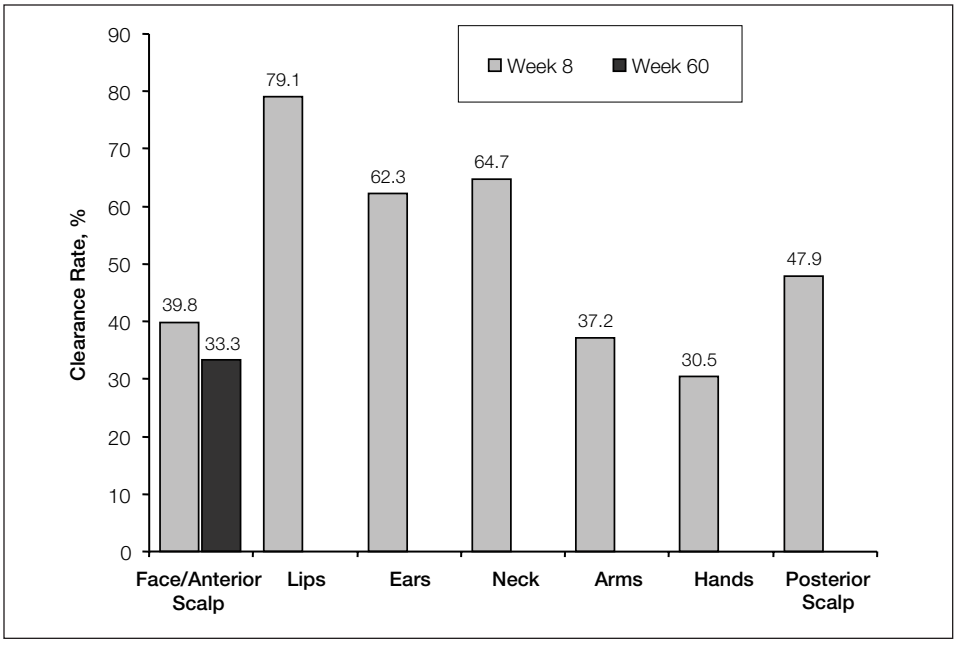

Figure 2. Clearance of actinic keratosis lesions at week 8 and week 60 (intention-to-treat population; N=277). Only face/anterior scalp actinic keratosis lesions were assessed after week 8.

added benefit to the overall management approach for treating AK. While patients may consider it an effective part of treatment, it has no direct effect on the reduction/elimination of AK lesions and did not affect the efficacy analyses within the study.

Conclusion

Participants undergoing one or two 4-week cycles of treatment with fluorouracil cream 0.5% applied once daily experienced statistically significant reductions in the number of AK lesions on the face/anterior scalp, lips, ears, neck, arms, hands, and/or posterior scalp during TC1 and TC2 (*P*<.0001). These reductions compared with baseline were maintained for up to 18 months. Clearance of AK lesions at week 8 was achieved in more than 62% of participants with lesions on the lips, ears, and neck, with total clearance of face/anterior scalp AK lesions occurring at a similar rate at the end of TC1 (40%) and TC2 (33%).

These study results provide further evidence that fluorouracil cream 0.5%, formulated using a patented microsponge delivery system, is a well-tolerated and effective therapy for AK lesions across multiple body sites. In addition, a stabilization effect was observed over time with respect to the incidence of irritation, confirming that increases in irritation do not directly correlate with increases in treatment efficacy.

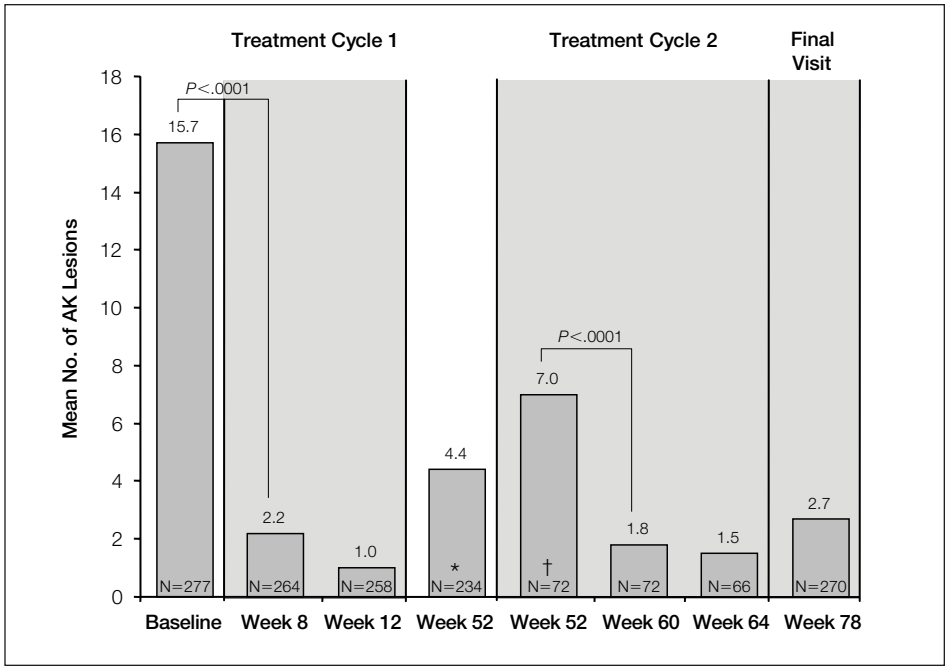

Figure 3. Mean number of face/anterior scalp actinic keratosis (AK) lesions throughout the course of the study (intention-to-treat population). Asterisk indicates participants with lesions who were not treated during treatment cycle 2 because they did not have lesions that required treatment or they refused treatment; dagger, participants who received treatment during treatment cycle 2.

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