These results are supplied for informational purposes only.

Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00377273
		Study Code:	DL6025-0201
Generic drug name:	5-Fluorouracil	**Date:**	09/Aug/2007

Title of the study:

An Open-label 18-Month Safety Study of Carac Cream (DL6025-Fluorouracil Cream 0.5%) for the Treatment of Actinic Keratoses

Investigators:

A total of 25 investigators across 25 study centers participated in the study.

Study Center(s):

A total of 25 study centers participated in the study

Publications (reference):

not applicable

Study period (years):	October 2003 to November 2005	**Clinical Phase:**	IV

Objectives:

The primary objective of the study was to assess the safety of Carac for the treatment of actinic ketatoses (AK) lesions on the face (including anterior scalp) and on other body sites by collecting adverse event (AE) data, including application site reactions and eye irritations.

Secondary objectives of the study were to:

- assess the reduction in the number of AK lesions and clearance of AK lesions on other body sites (posterior scalp, ears, neck, lips, arms and/or hands) and face (including anterior scalp, if applicable) after Carac treatment;
- measure the recurrence of facial AK lesions and assess the need for re-treatment of facial AK lesions at 12 months post initial treatment with Carac; and
- measure the recurrence of facial AK lesions 6 months after the second Carac treatment cycle (18 months after initial Carac treatment).

Methodology:

This was an open-label, multicenter study that consisted of two treatment/observation cycles and a final study visit. During the first treatment cycle, Carac was applied once daily to the patient's designated AK lesion treatment area (posterior scalp, ears, neck, lips, arms and/or hands and face [including anterior scalp, if applicable]) for up to 4 weeks as tolerated, followed by a 4-week follow-up period. Patients returned to the study center at the end of treatment and again 4 weeks after the last treatment application (follow-up visit). At the follow-up visit, a lesion count was performed and any residual lesions were treated with liquid nitrogen. All patients who had residual lesions treated with liquid nitrogen returned to the study center 4 weeks after treatment with liquid nitrogen and lesions were assessed and a biopsy was performed on persistent suspicious lesions. Patients returned to the study center 12 months after the first application of Carac and only those patients who had

visible or palpable lesions present on the face or anterior scalp were re-treated with once daily applications of Carac for up to 4 weeks. Visible or palpable AK lesions on other body areas were treated with liquid nitrogen. Patients returned to the study center at the end of treatment and 4 weeks after the last application of Carac. A count of AK lesions was performed and any remaining lesions were treated with liquid nitrogen. Patients who did not have facial or anterior scalp lesions at their visit for Treatment Cycle 2 were scheduled to return in 6 months for evaluation and all patients who had any remaining facial lesions treated with liquid nitrogen returned to the study center 4 weeks after the last liquid nitrogen treatment. All patients returned to the study center 6 months after the start of Treatment Cycle 2 for the end of study evaluation (18 months after the first application of Carac) and any lesions present were counted and patients received non-protocol treatment as per normal clinical practice. Adverse events, including application site reactions and eye irritation were collected throughout the study.

Number of Subjects:

Approximately 250 patients were planned for enrollment and 277 patients were actually enrolled into the study.

Main diagnosis & criteria for inclusion:

Males or females at least 18 years of age who had at least five visible and/or palpable AK lesions on the posterior scalp, ears, neck, lips, arms and/or hands and an additional five visible and/or palpable AK lesions on the face (including anterior scalp, if applicable).

Test product, dose and mode of administration, batch N°.:

Carac (Dermik Laboratories, Inc. DL6025 – fluorouracil 0.5% cream) applied topically to the designated treatment area once daily.

Duration of treatment:

Planned duration of the study: 24 months

Planned enrollment duration: up to 6 months

Reference therapy, dose and mode of administration, batch N°.:

No reference therapy was included in the study.

Criteria for evaluation:

Efficacy Parameters: The primary efficacy parameters were the reduction in the number of AK lesion counts and the percentage of patients who had clearance of AK lesions on the posterior scalp, ears, neck, lips, arms and/or hands after Treatment Cycle 1 at Week 8 and the percentage of patients who had clearance of AK lesions of the posterior scalp, ears, neck, lips, arms and/or hands after Treatment Cycle 1 at Week 8.

Secondary efficacy endpoints were:

- the reduction in AK lesion counts of the face (including anterior scalp, if applicable) after Treatment Cycle 1 at Week 8 and after Treatment Cycle 2 at Week 60;
- the percentage of patients who had clearance of facial AK lesions (including anterior scalp) after Treatment Cycle 1 at Week 8 and after Treatment Cycle 2 at Week 60; and
- the percentage of patients with recurrence of facial AK lesions (including anterior scalp) 12 months after initial Carac treatment at Week 52 and 6 months after Treatment Cycle 2 at Week 78.

Photographs of AK lesions were obtained at selected study centers at Baseline, at the end of treatment for each treatment cycle, Week 4 post-treatment visits for both treatment cycles, Treatment Cycle 2 (12-month Visit), and at the final study visit (18-month Visit).

Safety Parameter: Safety, the primary objective of the study, was assessed by summarizing the incidence of AEs, including all application site reactions and eye irritation during each treatment cycle and post-treatment at more than 30 days after the last study cycle treatment

After AK lesions were counted, a biopsy was performed for any persistent lesion considered suspicious by the investigator during the study.

Statistical methods:

Summary statistics were performed for all safety parameters. Changes and percent changes from Baseline in AK lesion counts were analyzed using a t-test. Summaries by designated body site and face were generated. An interim analysis was performed when all enrolled patients completed Treatment Cycle 1. Summaries were generated for safety parameters and baseline/demographic variables. Statistical analysis of efficacy endpoints was carried out at 5% level of significance.

Summary:

- **Efficacy results**

A statistically significant (p<0.0001) decrease in the number of AK lesions was observed following once daily application of Carac for up to 4 weeks (Treatment Cycle 1, Week 8). The mean percent decrease from Baseline to Week 8 was similar for AK lesions of the lips, ears, neck, and posterior scalp (range: -76.60 to –79.99) and statistically significant (P<0.0001) mean percent decreases in AK lesion counts of 62.82% and 56.47% were observed for the arm and hand body sites.

The majority of patients were clear of AK lesions on the lips (79.1% [95% CI: 64, 90]), ears (62.3% [95% CI: 54, 70]), and neck (64.7% [95% CI: 54, 75]) at Week 8 and approximately half the patients (47.9% [95% CI: 39, 57]) were clear of lesions on the posterior scalp at Week 8. Clearance rates of AK lesions of the arms (37.2% [95% CI: 30, 45]) and hands (30.5% [95% CI: 24, 37]) were observed in approximately one third of patients.

A statistically significant (p<0.0001) decrease in the mean percent change in the number of facial (including anterior scalp) AK lesions was observed from Week 52 to Week 60 post-treatment at Treatment Cycle 2, with a mean percent decrease of 64.92% from Week 52 to Week 60. Overall, A reduction in the number of AK lesions was observed for all designated treatment areas after 4 weeks of daily Carac application at the end of Treatment Cycle 1 (Week 12) and after a second treatment cycle (Weeks 52 to 64). In addition, the number of patients with recurrences of AK facial lesions decreased from Week 52 (54 [58.7%]) to Week 78 (11 [45.8%]).

- **Safety Results**

Overall, with the exception of the expected application site reactions and eye irritations, the incidence of treatment-emergent AEs was low and no unexpected AEs were reported. The most common treatment-emergent AEs reported during the study were related to application of Carac to the lesion site. Symptoms of these application site reactions included dryness, erythema, burning, erosion, pruritis, edema, and pain and symptoms of eye irritayion included watering, burning, itching, sensitivity, and stinging. Most AEs were mild or moderate in intensity.

A total of 17 (6.1%) patients experienced an SAE during Cycle 1, 7 (7.1%) patients experienced an SAE during Treatment Cycle 2, and 68 (24.5%) patients experienced an SAE more than 30 days after the end of Cycle 1 and Cycle 2. Carcinoma of the skin was the most common SAE, reported for 11 (0.4%) patients during Cycle 1, 5 (5.1%) patients during Treatment Cycle 2, and by 68 (24.5%) patients more than 30 days after Cycle 1 and Cycle 2.

Five patients discontinued treatment because of an AE; two during Treatment Cycle 1 and three patients during the Posy-treatment Cycle (more than 30 days after the end of treatment for either treatment cycle). Only one of these events (conjunctivitis) was considered related to study medication.

Two patient deaths were reported during the study; one due to heart arrest and one due to carcinoma. Both deaths occurred more than 30 days after the last application of study medication and both deaths were considered unrelated to study medication.

- **Date of report:: 23Jan2007**