CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-005

STATISTICAL REVIEW(S)

STATISTICAL/CLINICAL REVIEW AND EVALUATION.

ADDENDUM

AUG 11 1999

NDA#: 21-005

Applicant: Quintiles on behalf of Hyal

Name of Drug: 3% Diclofenac (Solarase) gel

Documents Reviewed: Volumes 1.1, 1.80-1.136, dated October 23, 1998

Type of Report: NDA review

Indication: Treatment of actinic keratosis

Medical officer: Hon-Sum Ko, M.D. (HFD-540)

INTRODUCTION

This Addendum reviews Study CT1101-01 at the request of the medical officer. Study CT1101-01 was not originally considered as one of the "pivotal" trials. Since Study CT1101-07 failed to reach significance for superiority of the active over placebo, Study CT1101-01 may be used as "confirmatory evidence" to support the efficacy claim. The treatment period (12 weeks) in CT1101-01 is similar to that in CT1101-07 (90 days), and there is a post treatment follow-up in Study CT1101-01.

The objective of Study CT1101-01 is to demonstrate that 3% diclofenac gel, administered BID for 12 weeks, is safe and effective in treatment of actinic keratosis (AK) compared to vehicle. Throughout this review, the abbreviations diclofenac, Study 01, Study 03, Study 04, and Study 07 will be used instead of 3% diclofenac gel, Study 1101-01, Study CT-1101-03, Study CT-1101-04, and Study CT-1101-07, respectively.

DESIGN

Study 01 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted at three dermatology clinics in Australia (from 10.13.94 to 6.25.95). Outpatients with actinic keratosis (AK) lesions on the head, neck, hands and arms were enrolled. Before treatment, the investigator identified a 25 cm^2 anatomical site with actinic keratoses which was designated as the study area. Patients were required to apply 0.25 grams to this area. (For comparison, patients in Studies 03, 04, and 07 applied 0.5 grams per 25 cm^2 area). Patient clinic visits were held at baseline and weeks 4, 8, and 12 with a 30-day post treatment follow-up. At baseline, the patients who met inclusion and exclusion criteria were randomized to treatment, either diclofenac or vehicle. The

physician assessed Baseline AK lesion severity and a lesion count was recorded.

EFFICACY:

The sponsor's protocol had 4 primary efficacy variables: actual lesion count change and percent change from baseline both at the end of treatment and at the 30-day post-treatment Follow-Up.

The Reviewer's comments on the efficacy analysis in this review:

In this review, the 30-day post-treatment Follow-Up visit (FU visit) is used as the primary efficacy timepoint. The primary efficacy population is the ITT population defined as all randomized patients. The primary efficacy variable is the proportion of patients free of actinic keratosis lesions at the 30-day post-treatment Follow-Up visit (as measured by the zero lesion count at the Follow-Up visit). Since this review uses a single primary efficacy variable (chosen by the reviewer before looking at the study results), no p-value adjustment for multiple comparisons is required. Change from baseline to the 30-day post-treatment Follow-Up visit in the lesion count is used as a secondary efficacy variable.

Statistical Analysis

Student t-test was used to compare two treatment groups at baseline relative to age, lesion number, and duration of treatment. A chi-square test was used to compare two treatment groups at baseline relative to sex, baseline lesion severity (mild, moderate, and severe), and anatomic area (head, neck, hands, and arms).

For the primary efficacy analysis, a CMH test adjusted for center was used to compare two treatment groups relative to the proportion of patients free of AK lesions at the 30-day post-treatment Follow-Up visit. For the secondary efficacy analysis, the Wilcoxon rank sum test adjusted for center and other covariates was used to compare two treatment groups relative to the change from baseline to F-U visit in the lesion count. A continuity adjusted Chi-Square test was used to compare proportions of patients with adverse events.

RESULTS of STUDY 01

DISPOSITION of PATIENTS

A total of 151 patients were randomized. One diclofenac patient (#092 in center 2) was found to be ineligible to participate because the lesions were determined not to be AK. This occurred prior to treatment being administered. Total of 150 (73 diclofenac and 77 vehicle) patients applied study treatment and were included in the safety analysis. Of them, 50 (68%) diclofenac and 65 (84%) vehicle patients completed all study visits (p=0.025). Of the 36 patients who did not completed all visits, 16 (22%) diclofenac and 3 (4%) vehicle patients withdrew from the study due to adverse events (p=0.002), 2 (3%) patients in each group withdrew for protocol violations (p=1.0), and 2 patients in each group requested withdrawal.

The ITT population in this review includes all 151 randomized at baseline patients. Of them, 74 patients were treated with diclofenac and 77 were treated with vehicle. Table 1 presents patient disposition at baseline by center.

Table 1. ITT population of Study 01 by center			
	Diclofenac	Vehicle	Total
Center 1	32	32	64
Center Site 2	31	32	63
Center Site 3	11	13	24
3 center combined	74	77	151

There was no statistically significant difference between two treatment groups at baseline relative to age (p=0.3), baseline lesion number (p=0.2), duration of treatment (p>0.2), sex (p=0.85), anatomic area (p=0.5), and baseline severity (p=0.078). The racial composition of the study population was not presented in the study report.

EFFICACY RESULTS in STUDY 03

Primary efficacy analysis

The primary efficacy population is the ITT population. The primary efficacy variable is proportion of patients free of AK lesions at 30-day post-treatment Follow-Up visit. Of the 151 patients in the ITT population, only 45 diclofenac and 42 vehicle patients had the 30-day post treatment visit (p=0.4). Table 2 shows number and % of patients free of AK lesions at the 30-day post-treatment Follow-Up visit in the ITT population of Study 01. In all three centers combined, 17 (23%) of diclofenac patients and 4 (5%) vehicle patients were clear of AK lesions at the 30-day post-treatment visit. As is seen from Table 2, diclofenac was statistically significantly better (p=0.002) than vehicle relative to the primary efficacy variable, proportion of patients free of lesions as measured by the proportion of patients with zero lesion count at the 30-day post-treatment Follow-Up visit. The Breslow-Day test for homogeneity across the centers was not statistically significant (p=0.96).

Table 2. Number (percent) of patients in the ITT population of Study 01 with zero AK lesion count at the 30-day post treatment Follow-Up.			
	Diclofenac	Vehicle	P-value*
Center 1	6/32 (19%)	1/32 (3%)	0.002
Center 2	8/31 (26%)	2/32 (6%)	
Center 3	3/11 (27%)	1/13 (8%)	
All 3 Centers combined	17/74 (23%)	4/77 (5%)	
* CMH test adjusted for center (homogeneity test p=0.96)			

Secondary efficacy analysis

Relative to the secondary efficacy variable, mean change from baseline in lesion count at the 30-day post-treatment follow-up, there was a statistically significant difference between diclofenac (6.2) and vehicle (2.4) with $p<0.001$. The center effect was highly significant ($p<0.001$) with the first center showing higher lesion count reduction than the other centers. However the positive trend of diclofenac over vehicle was found across all centers.

SAFETY in STUDY 01

Of the 151 patients randomized at baseline, 150 patients applied study treatment and were included in the safety analysis. Of the 73 diclofenac patients and 77 vehicle patients in the safety population, 16 (22%) diclofenac and 3 (4%) vehicle patients withdrew from the study due to adverse events ($p=0.002$). Table 3 compares the two treatment groups relative to adverse events with incidence rate greater than 3%.

Table 3. Number (percent) of patients in Study 01 who had at least one adverse event

Adverse event	Diclofenac (N=73)	Vehicle (N=77)	p-value
Skin and appendages	11 (15%)	4 (5%)	0.08
Dry skin	16 (22%)	2 (3%)	0.001
Edema	7 (10%)	3 (4%)	0.29
Pruritus	16 (22%)	6 (8%)	0.027
Rash	21 (29%)	7 (9%)	0.004

REVIEWER'S CONCLUSIONS on STUDY CT1101-01 (which may be conveyed to the sponsor):

Study CT1101-01 was a randomized, multicenter, parallel-group, placebo-controlled trial to compare efficacy and safety of 3% diclofenac gel (Solarase) and its vehicle administered twice daily for 12 weeks in the treatment of patients with actinic keratosis lesions. In this review, the primary efficacy population is the ITT population including all 151 randomized patients (74 on diclofenac and 77 on vehicle). This reviewer uses the 30-day post-treatment follow-up visit as the primary efficacy timepoint. In this review, the primary efficacy variable is the proportion of patients free of actinic keratosis lesions at the 30-day post-treatment follow-up visit. The secondary efficacy variable is the change from baseline to the 30-day post-treatment visit in the lesion count. Since this review uses a single primary efficacy variable (chosen by the reviewer before looking at the study results), no p-value adjustment for multiple comparisons is required.

Efficacy: The primary efficacy analysis of Study CT1101-01 shows that 3% diclofenac gel is statistically significantly better ($p=0.002$) than its vehicle relative to the proportion of patients free of actinic keratosis lesions at the 30-day post-treatment follow-up visit. The analysis of the secondary efficacy variable, the change from baseline to the 30-day post-treatment visit in the lesion count, supports the primary efficacy analysis with $p<0.001$.

Safety: The safety analysis of Study CT1101-01 shows that vehicle had a better safety profile than diclofenac: 16 (22%) diclofenac patients compared to 3 (4%) vehicle patients withdrew from the study due to adverse events (p=0.002). Statistically significantly more diclofenac patients had dry skin (p=0.001), pruritus (p=0.027), and rash (p=0.004).

Overall Conclusion: Study CT1101-01 supports the claim that 3% diclofenac gel administered twice daily for 12 weeks is statistically significantly more effective than vehicle in the treatment of patients with actinic keratosis. This is a matter of the clinical judgement of the reviewing medical division to decide whether 3% diclofenac gel should be approved given the safety issues described above.

/S/ 08.05.99

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics III

/S/ Aug 11, '99

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, Biometrics III

cc:
Archival NDA 21-005, Addendum
HFD-540
HFD-540/Mr. White
HFD-540/Dr. Wilkin
HFD-540/Dr. Ko
HFD-725/Dr. Huque
HFD-725/Dr. Srinivasan
HFD-725/Dr. Freidlin
HFD-344/Dr. Carreras
Chron. (HFD-725)
This review contains 5 pages.
wordfile\solarase\addendum\07-28-99

APPEARS THIS WAY
ON ORIGINAL

JUN - 7 1999

STATISTICAL/CLINICAL REVIEW AND EVALUATION.

NDA#: 21-005

Applicant: Quintiles on behalf of Hyal

Name of Drug: 3% Diclofenac (Solarase) gel

Documents Reviewed: Volumes 1.1, 1.86-1.136, dated October 23, 1998

Type of Report: NDA review

Indication: Treatment of actinic keratosis

Medical officer: Hon-Sum Ko, M.D. (HFD-540)

INTRODUCTION

The sponsor submitted reports of three Phase 3 trials, CT-1101-03, CT-1101-04 and CT-1101-07, to support the claim of the safety and efficacy of 3% Diclofenac gel in the treatment of patients with actinic keratosis (AK). The objective of these trials is to demonstrate that 3% Diclofenac gel, administered BID for 30-90 days, is safe and effective in treatment of AK compared to vehicle. Throughout this review, the abbreviations Diclofenac, Study 03, Study 04, and Study 07 will be used instead of 3% Diclofenac gel, Study CT-1101-03, Study CT-1101-04, and Study CT-1101-07, respectively. The three studies had similar designs with the major differences that Study 07 had only one site, Studies 03 and 04 had the treatment period of 90 days, and Study 04 had the treatment period of either 30 or 60 days in each site. In this review, multicenter Studies 03 and 04 will be considered as pivotal and a single-center Study 07 as supporting.

DESIGN

Study 03 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Outpatients with a clinical diagnosis of 5 or more actinic keratoses (AK) lesions were enrolled. An initial Screening Visit (Visit 1, Day -6) was conducted to assess patient demographics, medical history, and perform a limited physical examination. At Visit 2 (Day 1), the patients were randomized to treatment, either Diclofenac or Vehicle. Baseline AK lesion clinical severity was assessed by the physician and a lesion count was recorded.

Following randomization at Visit 2, patients visited the clinic on 2 occasions, at the 30-day intervals. These were Visits 3 and 4 (Days 30 and Day 60 post-randomization, respectively). Lesions were assessed by the investigator as at Visit 2 but if any new lesions were to appear then these were counted separately. Patients self-reported on their perception of the status of their lesions and were

queried in a general, non-specific way about the occurrence of any adverse events.
Thirty days (30) after Visit 4, the End of Treatment Visit (Visit 5, Day 90) was undertaken.
Thirty (30) days after Visit 5, patients returned to the clinic for the Follow-Up Visit 6 and lesions were evaluated by the physician. Any patient who withdrew from the study, was asked to return to the clinic 30 days after such withdrawal for the Follow-Up Visit.

Patients were randomized to Diclofenac or Vehicle at the 1:1 ratio. Treatment consisted of two topical applications, at least 6 hours apart, of study medication for each 5 cm x 5 cm treatment block, for 90 days. If and when all lesions completely resolved, as detected by the investigator, in any given treatment block, application of the study medication was terminated in that specific block. If all lesions in all (up to 3) treatment blocks completely resolved, the patient was considered to have progressed to Visit 5. The use of the study medication was stopped in all blocks at that time and the patient completed the Visit 5 procedures and was instructed to return for the 30 Day Follow-Up Visit.

EFFICACY:

Five or more AK lesions contained in up to 3 treatment blocks located in one or more of the Major Body Areas (MBAs) were eligible for evaluation. The MBAs were: forehead, central face, scalp, neck, back of hands, and arms.

Lesion Assessment

At each visit from Visit 2 (Day 1) through to Follow-Up, the following evaluations were made:

- TARGET LESION NUMBER SCORE (TLNS), the lesion count of only those lesions identified for treatment at Baseline.
- NEW LESION NUMBER SCORE (NLNS), the lesion count of those lesions not present at Baseline.
- CUMULATIVE LESION NUMBER SCORE (CLNS), the lesion count including both those lesions identified for treatment at Baseline and New lesions (CLNS=TLNS + NLNS).
- INVESTIGATOR'S GLOBAL IMPROVEMENT INDEX (IGII), was the scale used to score the investigator's perception of the improvement of the severity of patient's AK lesions during treatment. The IGII was completed at Visits 3 through Follow-Up. Scores were:

-2 - significantly worse, significantly more lesions, or majority of lesions increased in size, coarseness, and thickness of scales
-1 - slightly worse, more lesions, or some lesions increased in size, coarseness, and thickness of scales
0 - no change, essentially no change in lesion status
1 - slightly improved, some lesions cleared and scales have decreased in thickness, however, most lesions remain unchanged
2 - moderately improved, many lesions have cleared and scales have decreased in thickness
3 - significantly improved, majority of lesions absent and remaining scales barely perceptible on palpation

4 - completely improved, lesions cleared completely, adherent scaling plaques no longer evident on surface upon palpation, lesions no longer perceptible to touch, but slight pink or red foci may be visible at lesion site

The primary efficacy variables:

The **primary** efficacy endpoints in the **sponsor's analysis** are: for ITT/LOCF,
TLNS = 0, proportion (%) of patients with zero scores in all MBAs at Follow-Up
CLNS = 0, proportion (%) of patients with zero scores in all MBAs at Follow-Up
IGII - proportion (%) of patients with "Complete Clearance" scores at Follow-Up
The **secondary** analyses were based upon the change scores in the TLNS and CLNS at Follow-Up. These were analyzed in order to support the findings of the primary analyses.

The Reviewer's Comment:

1. ***In this review, the Follow-Up visit (FU visit) is used as the primary efficacy timepoint. Only one primary efficacy variable is used in this review: Proportion of patients with "Complete Clearance" status as measured by CLNS=0 at FU visit.***
   Two secondary efficacy variables are used in this review: change from baseline to FU visit in the CLNS and Proportion of patients "Cleared" as measured by Investigator Global Improvement Index score of "Completely Improved (IGII=4) at FU visit.

2. ***Major body areas, Forehead, Central Face, Scalp, Neck, Back of Hand, and Arm/Forearm were divided into two major anatomic regions as follows:***
   a) Forehead, Central Face, Scalp, and Neck; and
   b) Back of Hand and Arm/Forearm.

A subgroup analysis, by the two major anatomic areas, for the Proportion of patients with "Complete Clearance" status as measured by CLNS=0 at FU visit, was conducted.

Statistical Analysis

Baseline treatment arm comparisons on nominal data (race, sex) used the Cochran-Mantel-Haenszel Test to allow adjustment for center effects. Ordinal contrasts were made using Van Elteren's Test. Two-way ANOVA, adjusting for center, was used to assess treatment group differences in age and height. The following baseline characteristics of the patient population were evaluated for between treatment balance: gender, age, race, skin type, hair color, baseline severity, and skin cancer history. The proportion of patients with CLNS=0 at Follow-Up was compared between treatment arms by the Logit model adjusting for center. For ANOVA model, treatment-by-center interactions were assessed and considered significant if p=0.1 or less. Homogeneity of variance was tested by Levine's test. If the Levine's test failed at 0.1, the data were rank transformed.

The primary efficacy analysis was made on the LOCF databases for the ITT population. ANOVA was employed to assess the differences in change in CLNS from Baseline to Follow-Up. The model employed was: Response = treatment effect + center effect + center-by-treatment interaction effect.

Adverse events were summarized using COSTART Terminology. Patients with more than one event within a body system were counted only once within the system for listings of frequency of occurrence of AEs.

RESULTS of STUDY 03

DISPOSITION of PATIENTS

A total of 120 patients were randomized. Sixty (60) patients were randomized to each of the two treatment arms, Diclofenac (D) and gel Vehicle (V) in four centers. Two patients (one from Diclofenac group and one from vehicle group) were dropped from the study analyses: one was involved in a motor vehicle accident and the other did not return for the follow-up visit. Of the 118 patients reporting administration of study medications, 96 (81%) completed all the study visits and 22 (19%) withdrew prematurely. Of the 96 patients, 45 (47%) were in the Diclofenac arm and 51 (53%) were in the Vehicle arm. The 118 patients made up the Intent to Treat (ITT) population on which the efficacy analysis was based. Of the 22 premature terminations, 14 (64%) were in the Diclofenac group and 8 (36%) were in the Vehicle group (p=0.24).

There was no statistically significant difference between the two treatment groups relative to gender (p=0.70), age (p=0.97), race (p=0.37), height (p=0.31), skin type (p=0.76), eye color (p=0.67), familial history of skin cancer (p=0.63), and baseline severity index (p=0.37). The Vehicle group had twice as many patients (27 vs. 14) with brown hair as the Diclofenac group. Three times as many Diclofenac patients had blonde hair as did Vehicle patients (15 vs. 5). The difference in distribution of hair color types between the treatment was statistically significant (p=0.037). Blondes were more frequent in the Diclofenac group, and this bias was not in favor of the Diclofenac treatment.

EFFICACY EVALUATIONS in STUDY 03

Primary efficacy analysis

The primary efficacy variable is proportion of patients with "Complete Clearance" status as measured by CLNS=0 at Follow-Up visit. Table 1 shows number and % of patients with CLNS=0 by visit. There was a statistically significant difference (p<0.001) between the two groups at Follow-Up visit.

Table 1. CLNS=0 by Visits (Number (%)) in the ITT population of Study 03

COMPLETE LESION CLEARANCE (CLNS=0); Number of patients (% of group)			
	TREATMENT GROUP		
VISIT	DICLOFENAC	VEHICLE	*p* value
3	0	0	1.000
4	0	1 (2)	0.270
5	24 (41)	13 (22)	**0.014**
FOLLOW-UP	27(47)	11 (19)	**<0.001**

Percent of subjects with CLNS=0 at Follow-Up by two major anatomic regions

Five major body areas, Forehead, Central Face, Scalp, Neck, Back of Hand, and Arm/Forearm were divided into two major anatomic regions as follows:

a) Forehead, Central Face, Scalp, and Neck; and
b) Back of Hand and Arm/Forearm.

Table 2. Number (%) of subjects with CLNS=0 at Follow-Up by two major anatomic regions (ITT population of Study 03)

Major Anatomic Region	Diclofenac Gel		Vehicle Gel		P-value
	N (%)	N total	N (%)	N total	
Forehead, Central Face, Scalp, and Neck	22 (52)	42	11 (26)	43	0.0127
Back of Hand and Arm/Forearm	10 (40)	25	4 (18)	22	0.11

Table 2 shows the number and percent of subjects with CLNS=0 at Follow-Up by two major anatomic regions. Diclofenac was statistically significantly better (p=0.0127) than Vehicle in the anatomic region including Forehead, Central Face, Scalp, and Neck. Diclofenac was only numerically better (p=0.11) than Vehicle in the anatomic region including Back of Hand and Arm/Forearm.

Secondary efficacy analysis in Study 03

Table 3 shows mean CLNS and change from baseline in CLNS, by visit. The Diclofenac group experienced a statistically greater decrease **in CLNS at Follow-Up** (p=0.009). The Treatment-by-Center interaction terms in the ANOVA model for the change from baseline was not statistically significant (p>0.2).

Table 3. CLNS by Visits (Mean (sd)) in the ITT population of Study 03

TREATMENT	BASELINE	VISIT 3	VISIT 4	VISIT 5	FOLLOW UP
DICLOFENAC	6.7 (2.2)	6.0 (3.9)	4.2 (2.8)	2.8 (4.2)	1.6 (2.1)
Change from baseline	-	-0.5 (3.7)	-2.4 (3.2)	-3.9 (4.9)	-5.1 (3.1)
VEHICLE	7.1 (2.2)	5.1 (2.6)	3.7 (2.5)	2.7 (2.4)	3.2 (2.7)
Change from baseline	-	-2.1 (2.4)	-3.4 (2.9)	-4.3 (3.3)	-3.9 (3.6)
p value	-	**0.017**	0.122	0.960	**0.009**

Table 4. Investigator Global Improvement Index (Number (%)) in the ITT population of Study 03

COMPLETE IMPROVEMENT - IGII (score=4)			
	TREATMENT GROUP		
VISIT	DICLOFENAC	VEHICLE	*p* value
3	2 (4)	0	1.000
4	1 (2)	1 (2)	0.270
5	24 (41)	13 (22)	**0.014**
FOLLOW-UP	27 (47)	11(19)	**<0.001**

Table 4 shows number and % of patients with **IGII score=4** (completely improved). The Investigator Global Improvement Index supported the CLNS evaluations. Diclofenac was statistically significantly better than Vehicle at the Follow-Up Visit ($p<0.001$).

SAFETY in STUDY 03

Of the 117 patients evaluable for safety, 52 of 58 (90%) Diclofenac and 48 of 59 (81%) Vehicle patients experienced one or more AEs during the study whether related to the medication or not ($p=0.2$). There were 10 Diclofenac and 2 Vehicle patients reporting events identified under Metabolic and Nutritional Disorders ($p=0.014$). There was no statistically significant difference between the two treatment groups relative to number of patients experiencing other adverse events by major COSTART Body System ($p>0.05$). The majority of AEs reported were dermally-related: 46 (79%) patients reported dermal AEs compared to 38 (64%) in the Vehicle group ($p=0.07$). Statistically significantly more patients in the Diclofenac group reported occurrence for such events as dry skin ($p=0.018$), rash ($p=0.027$), and erythema ($p=0.005$). For other events, such as application site reaction, rash vesiculobullous, and skin exfoliation, the difference between the two groups was marginally significant ($p\leq 0.086$) in favor of Vehicle. The most frequently reported dermal AEs are listed in Table 5.

Table 5. Most Frequent Dermal Adverse Events Reported in Study 03

COMMONLY REPORTED DERMAL ADVERSE EVENTS		
BODY SYSTEM	TREATMENT	
	DICLOFENAC n=58 n (% of group)	VEHICLE n=59 n (% of group)
Pruritus (p=0.5)	32 (55)	29 (49)
Application site reaction (p=0.086)	20 (34)	12 (20)
Dry Skin (**p=0.018**)	21 (36)	10 (17)
Rash (**p=0.027**)	19 (33)	9 (15)
Erythema (**p=0.005**)	15 (26)	4 (7)
Rash vesiculobullous (p=0.077)	3 (5)	0 (0)
Skin exfoliation (p=0.077)	3 (5)	0 (0)
Ulcer skin (p=0.077)	3 (5)	0 (0)

CONCLUSIONS on STUDY 03:

The efficacy analysis of Study 03 shows that Diclofenac is statistically significantly better than vehicle relative to the primary efficacy variable, proportion of patients with "Complete Clearance" status as measured by CLNS=0 at the Follow-Up visit ($p<0.001$). This result is supported by the secondary efficacy variables, mean change from baseline to Follow-Up visit in the CLNS ($p=0.009$) and Proportion of patients "Cleared" as measured by Investigator Global Improvement Index score of "Completely Improved" (IGII=4) at Follow-Up visit ($p<0.001$). The primary efficacy analysis is also supported by the analysis of the number of subjects with CLNS=0 at Follow-Up visit by two major anatomic regions. Relative to the proportion of patients with "Complete Clearance" status as measured by CLNS=0 at Follow-up, Diclofenac was statistically significantly better than Vehicle ($p=0.0127$) in the anatomic region including Forehead, Central Face, Scalp, and Neck. In the anatomic region including Back of Hand and Arm/Forearm, Diclofenac was numerically better than Vehicle ($p=0.11$).

The safety analysis of Study 03 shows that there was no statistically significant difference between the treatment groups with respect to the number of patients experiencing adverse events within COSTART Body System categories with one exception: ten Diclofenac and two Vehicle patients reported Metabolic and Nutritional Disorders ($p=0.014$). The majority of adverse events reported were dermally-related: 46 (79%) patients reported dermal adverse events compared to 38 (64%) in the Vehicle group ($p=0.07$). Statistically significantly more patients in the Diclofenac group reported occurrence for such events as dry skin ($p=0.018$), rash ($p=0.027$), and erythema ($p=0.005$). For other events, such as application site reaction, rash vesiculobullous, and skin exfoliation, the difference between the two groups was marginally significant ($p\leq 0.086$) in favor of Vehicle.

RESULTS of STUDY 04

Study 04 was a multicenter, randomized, placebo-controlled, double-blind study conducted in 6 centers across Canada to evaluate the efficacy and safety of 3% Diclofenac gel versus the gel Vehicle. Eligible Actinic Keratosis patients were assigned randomly in a 1:1:1:1 ratio to 1 of 4 treatment groups: Active 30-day, Vehicle 30-day, Active 60-day or Vehicle 60-day. The Vehicle 30-day group served as a control for the Active 30-day group; the Vehicle 60-day group served as a control for the Active 60-day group; and the Vehicle Treatment Arm (all patients on Vehicle treatment) served as a control for the Active Treatment Arm (all patients on Active treatment).

Table 6. Patient Disposition by Treatment Arm in Study 04

Treatment Arm	Number (Percent) of Patients		
	Randomized	Withdrawn	Completed
Active (30 and 60 day)	97 (50)	8 (4)	89 (46)
Vehicle (30 and 60 day)	98 (50)	3 (2)	95 (48)
Total	195 (100)	11 (6)	184 (94)

Of the 195 patients randomized, there were 8 withdrawals in the Active group and 3 in the placebo group (p= 0.117). Patient disposition by treatment arm is shown in Table 6.

EFFICACY RESULTS in STUDY 04

The ITT with last observation carried forward (ITT/LOCF) was the primary efficacy analysis. All of the 195 randomized patients received at least one dose of the study medication. The ITT population was evenly distributed across each of 4 Treatment Groups, both overall and by Center.

The baseline disposition refers to the ITT population for all 30 or 60 day patients. All 195 randomized patients were Caucasians. There was no statistically significant difference between treatment groups relative to age (p=0.12), gender (p=0.26), height (p=0.33), weight (p=0.18), systolic or diastolic blood pressure (p>0.43), heart rate/pulse (p=0.59), hair color (p=0.84), eye color (0.39), skin cancer history (p=0.42), baseline severity index, and distribution of major body areas (p=0.98). Two methods were used to assess skin type: quantitative and Fitzpatrick scale. The difference between the two treatment groups was statistically significant relative to quantitative skin type (p=0.006) and marginally significant relative to the Fitzpatrick scale (p=0.08).

Analysis of covariance (ANCOVA) was done using Skin Type and the Fitzpatrick Score as a covariate in the analyses of change from baseline in the mean CLNS. There were no significant interaction terms for Skin Type (p=0.25) or Fitzpatrick Score (p=0.63). Therefore, these covariates were not included in the primary efficacy analysis.

Primary Efficacy Analysis in Study 04:

Complete Resolution of Lesions: CLNS = 0

The primary efficacy analysis used the ITT /LOCF study population. Table 7 shows the number of patients in each of the 4 treatment groups along with Active to Vehicle contrast p-values:

For the 30-day Treatment Groups, at Follow-Up visit, 7 (14%) and 2(4%) patients respectively in the Active and Vehicle 30 day Treatment Groups presented with CLNS=0 (p=0.22). For the 60-day Treatment Groups, the treatment difference was statistically significant at Follow-Up visit [Active (15/48=31%) and Vehicle (5/49=8%)] (p=0.0214).

For all Active vs. Vehicle, the difference in the proportion of patients between the Active Treatment Arm (22/97=23%) and the Vehicle Treatment Arm (7/98=7%) was statistically significant from Baseline to Follow-Up with a p=0.016.

Table 7. Complete Lesion Clearance (CLNS=0) by Treatment Group and Arm in the ITT population of Study 04

Visit	30-day Treatment			60-day Treatment			Overall p-value
	Number (%)		p-value 30-day	Number (%)		p-value 60-day	A vs. V
	Active	Vehicle		Active	Vehicle		
Baseline	0/49	0/49	--	0/48	0/49	--	--
Visit 3/ EOT	3/49 (6)	0/49	0.4405	1/45 (2)	2/47 (4)	0.9130	0.6408
Visit 4/ EOT	--	--	--	6/48 (13)	7/49 (14)	0.9201	--
Follow-Up	7/49 (14)	2/49 (4)	0.2212	15/48 (31)	5/49 (8)	**0.0214**	**0.0156**

Percent of subjects with CLNS=0 at Follow-Up by two major anatomic regions

Five major body areas, Forehead, Central Face, Scalp, Neck, Back of Hand, and Arm/Forearm were divided into two major anatomic regions as follows:

c) Forehead, Central Face, Scalp, and Neck; and
d) Back of Hand and Arm/Forearm.

Table 8 shows the number and percent of subjects in both 30- and 60-day treatment groups combined with CLNS=0 at Follow-Up by two major anatomic regions.

Table 8. Number (%) of subjects with CLNS=0 at Follow-Up by two major anatomic regions (ITT population of Study 04)

Major Anatomic Region					P-value
	Diclofenac Gel		Vehicle Gel		
	N (%)	N total	N (%)	N total	
Forehead, Central Face, Scalp, and Neck	22 (26)	84	6 (7)	85	0.0017
Back of Hand and Arm/Forearm	2 (11)	18	2 (10)	20	0.913

As is seen from Table 8, relative to the proportion of patients with "Complete Clearance" status as measured by CLNS=0 at Follow-up, in the anatomic region including Forehead, Central Face, Scalp, and Neck, Diclofenac was statistically significantly better than Vehicle (p=0.0017). In the anatomic region including Back of Hand and Arm/Forearm, there was no difference between Diclofenac and Vehicle (p=0.91).

Secondary Analysis in Study 04

Table 9 shows the mean change in the CLNS from baseline. For the 30-day Treatment Groups, the contrast of mean ΔCLNS for Active (-3.9) and Vehicle (-1.7) was statistically significant at Follow-Up visit with p=0.0079. For the 60-day Treatment Groups, the difference in ΔCLNS from Baseline to Follow-Up visit was statistically significant ([Active -3.8 and Vehicle -1.7], p=0.0138). For all Active vs. Vehicle, at Follow-Up visit, the mean ΔCLNS comparison between the treatments was statistically significant at p=0.0003.

Table 9. Change in Cumulative Lesion Number Score (ΔCLNS) in the ITT population of Study 04

Baseline To Visit	30-day Treatment			60-day Treatment			
	Mean (SD)		30-day	Mean (SD)		60-day	p-value
	Active	Vehicle	p-value	Active	Vehicle	p-value	A vs. V
Visit 3/ EOT	-0.8(4.1)	-1.3(2.2)	0.6394	-0.1(5.7)	-1.4(2.7)	0.2784	0.2576
Visit 4/ EOT	--	--	--	-2.0(4.7)	-2.1(3.7)	0.9851	--
F/Up	-3.9(3.7)	-1.7(2.4)	0.0079	-3.8(3.4)	-1.7(3.3)	**0.0138**	**0.0003**

Table 10. IGII = 4, Investigator Assessed 'Completely Improved' Status by Treatment Group and Treatment Arm in the ITT population of Study 04

Baseline To Visit	30-day Treatment			60-day Treatment			Overall
	Number (%)		p-value	Number (%)		p-value	p-value
	Active	Vehicle	30-day	Active	Vehicle	60-day	A vs. V
Visit 3/ Day 30	3/49 (6)	0/49 (0)	0.4451	3/46 (7)	2/47 (4)	0.5740	0.3458
Visit 4/EOT	--	--	--	6/48 (13)	7/49 (14)	0.8954	--
F/Up	8/49 (16)	2/49 (4)	0.1344	15/48 (31)	5/49 (10)	**0.0213**	**0.0089**

Table 10 shows number and percent of patients with "Completely Improved " status as assessed by Investigator Global improvement index (IGII=4). For the 30-day Treatment Groups, at Follow-Up visit, there were 8 (16%) Active and 2 (4%) Vehicle patients who were classified by the Investigator as Completely Improved; this difference was not statistically significant with p=0.1344. For the 60-day Treatment Groups, at Follow-Up visit, there were 15 (31%) Active and 5 (10%) Vehicle patients who were scored by the Investigator as Completely Improved. This difference at Follow-Up was statistically significant at p=0.0213. For all Treatment Arms, overall the difference in the number of patients scoring IGII=4 between the Active (23/97, 24%) and Vehicle (7/98, 7%) Treatment Arms was statistically significant, p=0.0089.

SAFETY in STUDY 04

Of the 97 Diclofenac and 98 Vehicle patients, 5 Diclofenac and 2 Vehicle patients withdrew for AEs respectively (p=0.43). Overall the incidence of at least one reported AE for patients on the Active Treatment Arm was slightly lower (79/97=81%) than that for the Vehicle Treatment Arm (85/98=87%) with p=0.42. The most frequently reported dermal AEs were: pruritus, rash, dry skin, and application site reactions. The Diclofenac patients had a slightly higher incidence of rash, dry

skin, and application site reactions than their respective control groups (p>0.075). The incidence of pruritus was statistically significantly higher (p=0.001) in the Vehicle groups (58/98=59%) than in the Active groups (35/97=36%).

CONCLUSIONS for STUDY 04

The efficacy analysis of 60 day treatment groups in Study 04 shows that Diclofenac is statistically significantly better than Vehicle relative to the primary efficacy variable, proportion of patients with "Complete Clearance" status as measured by CLNS=0 at the Follow-Up visit (p=0.021). The efficacy analysis of 30 day treatment groups in Study 04 shows that Diclofenac is only numerically superior to Vehicle relative to the primary efficacy variable, proportion of patients with "Complete Clearance" status as measured by CLNS=0 at the Follow-Up visit (p=0.22).

The efficacy analysis of all Diclofenac patients versus all Vehicle patients of Study 04 shows that Diclofenac is statistically significantly better than Vehicle relative to the primary efficacy variable, proportion of patients with "Complete Clearance" status as measured by CLNS=0 at the Follow-Up visit (p=0.016).

These results are supported by the analysis of the secondary efficacy variables. Relative to the mean change from baseline to Follow-Up visit in the CLNS, the p-values are 0.0079, 0.0138, and 0.0003 for the 30 day treatment groups, 60 day treatment groups, and both groups combined. For the proportion of patients "Cleared" as measured by Investigator Global Improvement Index score of "Completely Improved" (IGII=4) at Follow-Up visit, the p-values are 0.1344, 0.0213, and 0.0089 for the 30 day treatment groups, 60 day treatment groups, and both groups combined.

The primary efficacy analysis is supported by the subgroup analysis of the number of subjects with CLNS=0 at Follow-Up visit in the anatomic region including Forehead, Central Face, Scalp, and Neck (p=0.0017). In the anatomic region including Back of Hand and Arm/Forearm, there was no difference between Diclofenac and Vehicle (p=0.91).

Safety analysis of Study 04 shows that the incidence of at least one adverse event for Diclofenac patients was similar (81%) to that for the Vehicle patients (87%) with p=0.42. The most frequently reported dermal adverse events were: pruritus, rash, dry skin and application site reactions. The Diclofenac patients had a numerically higher incidence of rash, dry skin, and application site reactions than their respective control groups (p>0.075). The incidence of pruritus was statistically significantly higher (p=0.001) in the Vehicle patients (59%) than in the Diclofenac patients (36%).

RESULTS in STUDY 07

A total of 112 patients were randomized. Fifty-six (56) patients were randomized to each of the two treatment arms, Diclofenac (D) and gel Vehicle (V). One vehicle patient was dropped from the study analyses due to being lost to follow up after the randomization visit. Of the 112 patients enrolled in the study, 93 (84%) completed all the study visits and 19 (16%) were reported to have withdrawn

prematurely. Of the 93 patients completed the study, 44 (47%) were in the Diclofenac arm and 49 (53%) were in the Vehicle arm (p=0.31). Of the 111 patients in the Intent-to-Treat (ITT) population, 44 Diclofenac and 49 Vehicle patients completed all visits (p=0.21). Eight Diclofenac and 3 Vehicle patients withdrew due to adverse events (p=0.20).

EFFICACY RESULTS in STUDY 07

The primary efficacy population was the Intent-to-Treat population (ITT) with the last observation available carried forward (LOCF). Of the 111 ITT evaluable patients, all were Caucasian. There was no difference between the treatment groups relative to height (p=0.86), weight (p=0.44), categorical scale skin type (p=0.65), Fitzpatrick skin type (p=0.48), skin cancer history, hair colour (p=0.89), and eye colour (p=0.76). The majority of patients were classified as having mild or moderate lesion severity. There were 5 (9%) Diclofenac and no Vehicle patients classified as having severe lesions at Baseline. The difference between treatment groups relative to baseline severity approached statistical significance (p=0.060) with the Diclofenac group having the more severe lesion scores at Baseline. The Diclofenac group reported a mean of 64 years of age compared to 68 years for the Vehicle treated group (p=0.038). There was also a statistically significant difference in the distribution of males and females between treatment groups (p=0.029) with more females and fewer males in the Diclofenac group .

Table 11 shows the results for the primary efficacy variable, the proportion of patients with "Complete Clearance "status as measured by CLNS=0 at Follow-Up visit. The Diclofenac group was numerically better (p=0.061) than the Vehicle group relative to the proportion of subjects with "Complete Clearance "status as measured by CLNS=0 at Follow-Up visit (34% vs. 18%).

Table 11. CLNS=0 by Visits (number of patients) for the ITT population of Study 07.

COMPLETE LESION CLEARANCE (CLNS=0)			
	TREATMENT GROUP		
Visit	**Diclofenac**	**Vehicle**	***p* value**
3	0/37	0/46	-
4	1/37	0/49	0.430
5	9/44	9/46	0.611
Follow-up	18/53 (34%)	10/55 (18%)	**0.061**

Percent of subjects with CLNS=0 at Follow-Up by two major anatomic regions

Five major body areas, Forehead, Central Face, Scalp, Neck, Back of Hand, and Arm/Forearm were divided into two major anatomic regions as follows:

e) Forehead, Central Face, Scalp, and Neck; and

f) Back of Hand and Arm/Forearm.

Table 12 shows the number and percent of subjects with CLNS=0 at Follow-Up by two major anatomic regions. As is seen from Table 12, relative to the proportion of patients with CLNS=0

at Follow-Up visit, Diclofenac was statistically significantly better (p=0.0078) than vehicle in the anatomic region including Forehead, Central Face, Scalp, and Neck. Diclofenac was numerically worse than vehicle in the anatomic region including Back of the Hand and Arm/Forearm (p=0.47).

Table12. Number (%) of subjects with CLNS=0 at Follow-Up by two major anatomic regions (ITT population of Study 07)

Major Anatomic Region					P-value
	Diclofenac Gel		Vehicle Gel		
	N (%)	N total	N (%)	N total	
Forehead, Central Face, Scalp, and Neck	17 (49)	35	7 (18)	38	0.0078
Back of Hand and Arm/Forearm	2 (10)	21	3 (18)	17	0.4675

Secondary efficacy analysis

Table 13 shows the mean change in the CLNS from baseline. As is seen from Table 11, Diclofenac was statistically significantly better than Vehicle relative to the mean change in the CLNS at the Follow-Up visit (p=0.006).

Table 13. Mean Change in Cumulative Lesion Number Score (mean ΔCLNS (SD)) by Visits in the ITT population of Study 07

TREATMENT	BASELINE	VISIT 3	VISIT 4	VISIT 5	FOLLOW UP
Diclofenac	9.2 (3.4)				
delta baseline	-	-1.2 (2.3)	-2.8 (3.5)	-5.1 (4.9)	-6.6 (4.2)
Vehicle	8.0 (2.2)				
delta baseline	-	-1.5 (2.6)	-2.9 (2.9)	-3.9 (3.3)	-4.5 (3.4)
***p* value**	-	0.542	0.907	0.138	**0.006**

Table 14 shows mean score in the Investigator Global improvement index (IGII). Diclofenac was statistically significantly better than Vehicle relative to Investigator improvement Index at Follow-Up visit (p=0.009).

APPEARS THIS WAY
ON ORIGINAL

Table 14. Investigator Global Improvement Index by Treatment Group and Treatment Arm in the ITT population of Study 07

MEAN IGII SCORE (sd)			
	TREATMENT GROUP		
Visit	Diclofenac	Vehicle	*p* value
3	0.7 (1.0)	1.0 (1.2)	0.144
4	1.1 (1.2)	1.5 (1.3)	0.184
5	2.1 (1.5)	1.7 (1.6)	0.192
Follow-up	2.7 (1.4)	1.9 (1.6)	**0.009**

SAFETY in STUDY 07

Table 15. Patients with Application Site Reactions (any level of causality)

COSTART Term	Number (%) of patients		
	Diclofenac N=56	Vehicle N=55	*p* value
Application Site Reaction	50 (89)	41 (75)	**0.043**
sub-categories of Application Site Reaction			
Contact dermatitis	30 (54)	3 (5)	**<0.0001**
Pruritus	28 (50)	23 (42)	0.387
Rash	24 (43)	8 (15)	**0.001**
Exfoliation	12 (21)	7 (13)	0.224

Of the 111 patients evaluable for safety, 52 of 56 (93%) Diclofenac and 45 of 55 (82%) Vehicle treated patients experienced one or more AEs (p=0.14). Statistically significantly more Diclofenac patients (51, 91%) experienced dermal adverse events compared with 41 (74%) Vehicle patients (p=0.039). Table 15 shows the number of patients with application site reactions. Statistically significantly more Diclofenac patients (50, 89%) experienced application site reactions compared with 41 (75 %) Vehicle patients (p=0.043). Specifically, 30 (54%) Diclofenac patients had contact dermatitis versus 3 (5%) Vehicle patients (p<0.0001). Twenty-four (43%) Diclofenac patients had rash versus 8 (15%) Vehicle patients with p=0.001.

CONCLUSIONS on STUDY 07

Primary efficacy analysis of Study 07 shows that Diclofenac is only numerically better than Vehicle: 34% of Diclofenac patients versus 18% Vehicle patients had "Complete Clearance" status as measured by CLNS=0 at the Follow-Up visit (p=0.061). In the anatomic region including Forehead, Central Face, Scalp, and Neck, Diclofenac was statistically significantly better than Vehicle relative to the proportion of patients with "Complete Clearance" status as measured by CLNS=0 at Follow-up (p=0.0078). In the anatomic region including Back of Hand and Arm/Forearm, Diclofenac was numerically worse than Vehicle (p=0.47).

Diclofenac was statistically significantly better than Vehicle relative the secondary efficacy variables, mean change from baseline to Follow-Up visit in the CLNS (p=0.006) and Investigator Global Improvement Index at Follow-Up visit (p=0.009).

Safety analysis of Study 07 shows that the incidence of at least one adverse event for Diclofenac patients was numerically greater (93%) than that for the Vehicle patients (82%) with p=0.14. Statistically significantly more Diclofenac patients (N=51, 91%) reported dermal adverse events compared to 41 patients (75%) in the Vehicle group (p=0.039). Statistically significantly more patients in the Diclofenac group reported application skin reaction (p=0.043), including contact dermatitis (p<0.0001) and rash (p=0.001).

INTEGRATED EFFICACY SUBGROUPS ANALYSIS (Studies 03, 04, and 07 combined)

Integrated subgroup analysis was performed to estimate effect of some covariates (age, gender, Baseline Severity Index, Fitzpatrick score, and Major Body Area) on the change in the lesion count. The covariate term was included in the ANOVA model. Assessed were the treatment term, covariate term and the treatment-by-covariate term.

The effect of **age** was assessed using two categories: $\leq$ 65 years and > 65 years. The treatment term was highly significant (p<0.0001), while both the age and age-by-treatment were not significant (p=0.2 and p=0.4, respectively).

The effect of **gender** was highly significant (p=0.0001), with male responding more favorably to both Diclofenac and Vehicle than females. The gender-by-treatment interaction term was not significant P=0.2). There was more than twice as great proportion of females (50%) with target lesions on their hands/arms than males (21%) in the Diclofenac group. The hands/arms do not appear to respond as well as face, forehead and scalp. The skewed distribution of MBAs between genders may influence the subgroup analysis by gender.

The effect of Baseline Severity Index (BSI) was assessed using three categories: mild, moderate, and severe. The BSI term was significant (p=0.010), but the BSI-by-treatment interaction term was not significant (p=0.81).

There was no relationship between lesion count and the Fitzpatrick score: the covariate and the treatment-by-covariate interaction terms were not significant (p=0.67 and p=0.33, respectively).

To evaluate the relationship between the lesion count and Major Body Area (MBA), two categories were used: hands/arms and non-hands/arms (other MBAs). There was the following distribution of MBAs between the treatment groups: 72% of Diclofenac treated sites and 73% of Vehicle treated sites were face, forehead and scalp. The MBA term was highly significant with p=0.0007 and the interaction term was also significant at p=0.09. The hands/arms area responded worse to Diclofenac treatment than the other MBAs treated.

Table 16 shows the results of the integrated subgroup analysis for the primary efficacy variable, proportion of patients with CLNS=0 at 30-days Post-Treatment Follow-Up. As is seen from Table 16, Diclofenac was statistically significantly better than vehicle in each of the two age groups (p<0.0036). Diclofenac was statistically significantly better than vehicle in males (p<0.0001) and statistically marginally better in females (p=0.063). Diclofenac was statistically significantly better than vehicle in the major anatomic region including forehead, central face, scalp, and neck (p<0.0001). However, Diclofenac was only numerically better than vehicle in the anatomic region including back of hand and arm/forearm (p=0.37).

Table 16. Integrated subgroup analysis for the proportion of patients with CLNS=0 at 30days Post-Treatment Follow-Up (ITT populations of Studies 03, 04, and 07 combined)

Subset	Treatment group				P-value
	Diclofenac Gel		Vehicle		
	Number of patients (%)	N total	Number of patients (%)	N total	
Males	51 (35%)	145	24 (14%)	168	<0.0001
Females	16 (25%)	63	4 (9%)	44	0.0634
≤ 65 years	30 (35%)	86	12 (13%)	90	0.0019
> 65 years	37 (30%)	122	16 (13%)	122	0.0036
Anatomical areas: forehead, central face, scalp, and neck	61 (38%)	161	24 (14%)	166	<0.0001
Anatomical areas: back of hand, arm/forearm	14 (22%)	64	9 (15%)	59	0.3689

INTEGRATED SAFETY ANALYSIS (Studies 03, 04, and 07 combined)

Of the 423 patients evaluable for safety in the three Phase 3 studies 03, 04, and 07, there were 211 Diclofenac treated patients and 212 Vehicle treated patients. Of them, 183 (87%) Diclofenac patients and 178 (84%) Vehicle patients experienced one or more AEs during the study (p=0.4). There was a statistically significant difference between treatment groups in favor of Vehicle relative to the number of patients with treatment interrupted due to AEs (9% vs. 2%, p=0.005), number of patients discontinued (18% vs. 4%, p=0.001), number of patients with related AEs (81%vs. 72%, p=0.04), and the number of patients with no action taken (p=0.03). Numerically

more Diclofenac patients (172, 82%) had skin AEs than Vehicle patients (160, 75%) with p=0.1. There was a statistically significant difference between the treatment groups relative to the following skin adverse events: contact dermatitis (22% vs. 3%, p=0.001), dry skin (23% vs. 14%, p=0.02), scaling (16% vs. 8%, p=0.02), and rash (39% vs. 18%, p=0.001). Table 17 shows some safety comparisons between treatment groups in the three Phase 3 studies combined.

Table 17. Integrated Safety Analysis (Studies 03, 04, and 07 combined)

Comparison	Treatment Group, N (%)		p-value
	Diclofenac, N=211	Vehicle, N=212	
Patients with one or more Adverse Events	183 (87%)	178 (84%)	0.4
No action taken	103 (49%)	126 (59%)	0.03
Treatment interrupted	18 (9%)	5 (2%)	0.005
Discontinued treatment altogether	38 (18%)	9 (4%)	0.001
Fatients with related Adverse Events	170 (81%)	153 (72%0	0.04
Dermal Adverse Events	172 (82%)	160 (75%)	0.1
Sub-Categories of Dermal Adverse Events			
Contact dermatitis	47 (22%)	6 (3%)	0.001
Dry skin	49 (23%)	30 (14%)	0.02
Scaling	33 (16%)	17 (8%)	0.02
Rash	83 (39%)	39 (18%)	0.001

REVIEWER'S CONCLUSIONS

The sponsor submitted three Phase 3 vehicle-controlled studies, 03, 04, and 07, to support the claim that Diclofenac is safe and effective in the treatment patients with actinic keratosis. In this review, the multicenter Studies 03 and 04 are considered as pivotal, and the single center Study 07 is considered supporting.

This reviewer used the following primary efficacy variable: proportion of patients with "Complete Clearance" status as measured by Cumulative Lesion Number Score (CLNS=0) at Follow-Up visit. Two secondary efficacy variables are used in this review: change from baseline to Follow-Up visit in the CLNS and Proportion of patients "Cleared" as measured by Investigator Global Improvement Index score of "Completely Improved (IGII=4) at Follow-Up visit.

Major body areas, forehead, central face, scalp, neck, back of hand, and arm/forearm were divided into two major anatomic regions as follows:

b) forehead, central face, scalp, and neck and
b) back of hand and arm/forearm.

A subgroup analysis, by the two major anatomic regions, for the Proportion of patients with "Complete Clearance" status as measured by CLNS=0 at Follow Up visit, was conducted for individual studies and for the three studies combined.

Efficacy

Efficacy results in Study 03

The efficacy analysis of Study 03 showed that Diclofenac was statistically significantly better than vehicle relative to the primary efficacy variable, proportion of patients with "Complete Clearance" status as measured by CLNS=0 at the Follow-Up visit ($p<0.001$). This result is supported by the secondary efficacy variables, mean change from baseline to Follow-Up visit in the CLNS ($p=0.009$) and Proportion of patients "Cleared" as measured by Investigator Global Improvement Index score of "Completely Improved" (IGII=4) at Follow-Up visit ($p<0.001$).

The efficacy subgroup analysis by two major anatomic regions showed that relative to the proportion of patients with "Complete Clearance" status as measured by CLNS=0 at Follow-up, Diclofenac was statistically significantly better than vehicle ($p=0.0127$) in the anatomic region including forehead, central face, scalp, and neck. In the anatomic region including back of hand and arm/forearm, Diclofenac was only numerically better than vehicle ($p=0.11$).

Efficacy in Study 04

The efficacy analysis of all Diclofenac patients versus all vehicle patients of Study 04 showed that Diclofenac was statistically significantly better than vehicle relative to the primary efficacy variable, proportion of patients with "Complete Clearance" status as measured by CLNS=0 at the Follow-Up visit ($p=0.016$).

This result is supported by the analysis of the secondary efficacy variables. Relative to the mean change from baseline to Follow-Up visit in the CLNS, Diclofenac was statistically significantly better than vehicle ($p=0.0003$). For the proportion of patients "Cleared" as measured by Investigator Global Improvement Index score of "Completely Improved" (IGII=4) at Follow-Up visit, Diclofenac was also statistically significantly better than vehicle ($p=0.0089$).

The primary efficacy subgroup analysis showed that Diclofenac was statistically significantly better than vehicle relative to the number of subjects with CLNS=0 at Follow-Up visit in the anatomic region including forehead, central face, scalp, and neck ($p=0.0017$). In the anatomic region including back of hand and arm/forearm, there was no difference between treatment groups ($p=0.91$).

Efficacy in Study 07

Primary efficacy analysis of Study 07 showed that Diclofenac was only numerically better than vehicle: 34% of Diclofenac patients versus 18% of vehicle patients had "Complete Clearance" status as measured by CLNS=0 at the Follow-Up visit ($p=0.061$). In the anatomic region including forehead, central face, scalp, and neck, Diclofenac was statistically significantly better than vehicle relative to the proportion of patients with "Complete Clearance" status as measured by CLNS=0 at Follow-up ($p=0.0078$). In the anatomic region including back of hand and

arm/forearm, Diclofenac was numerically worse than vehicle (p=0.47).

Diclofenac was statistically significantly better than vehicle relative the secondary efficacy variables, mean change from baseline to Follow-Up visit in the CLNS (p=0.006) and Investigator Global Improvement Index at Follow-Up visit (p=0.009).

Integrated Primary Efficacy Subgroup Analysis (Studies 03, 04, and 07 combined)

Two age subgroups were considered: $\leq$ 65 years and > 65 years. In each of the age subgroups, Diclofenac was statistically significantly better (p<0.0036) than vehicle relative to the primary efficacy variable, proportion of patients with "Complete Clearance" status as measured by CLNS=0 at the Follow-Up visit. Efficacy analysis by race was not performed because more than 99% of patients were Caucasians.

There was the following distribution of major anatomic regions between the treatment groups: 72% of Diclofenac treated sites and 73% of vehicle treated sites were face, forehead and scalp. The major anatomic region term in the ANOVA model was highly significant (p=0.0007) and the region-by-treatment interaction term was also significant (p=0.09). The primary efficacy subgroup analysis relative to the proportion of patients with "Complete Clearance" status as measured by CLNS=0 at the Follow-Up visit, showed that Diclofenac was statistically significantly better than vehicle in the anatomic region including forehead, central face, scalp, and neck (p<0.0001). Diclofenac was only numerically better than vehicle in the anatomic region including back of hand and arm/forearm (p=0.37).

Primary efficacy subgroup analysis by gender showed that Diclofenac was statistically significantly better than vehicle in males (p<0.0001) and statistically marginally better in females (p=0.063). The effect of gender in the ANOVA model was highly significant (p=0.0001), with male responding more favorably to both Diclofenac and vehicle than females. The gender-by-treatment interaction term was not significant (p=0.2). The reason for the different treatment response by males and females may be due to the fact that there was more than twice as great proportion of females (50%) with target lesions on their hands/arms than males (21%) in the Diclofenac group. As the hand/arms responded worse than face, forehead and scalp, the skewed distribution of major anatomic regions between genders may influenced the different treatment response in males and females.

Safety

The safety analysis of Study 03 showed that there was no statistically significant difference between the treatment groups with respect to the number of patients experiencing adverse events within COSTART Body System categories with one exception: ten Diclofenac and two vehicle patients reported Metabolic and Nutritional Disorders (p=0.014). The majority of adverse events reported were dermally related: 46 (79%) patients reported dermal adverse events compared to 38 (64%) in the vehicle group (p=0.07). Statistically significantly more patients in the Diclofenac group reported occurrence for such events as dry skin (p=0.018), rash (p=0.027), and erythema (p=0.005). For other events, such as application site reaction, rash vesiculobullous, and skin

exfoliation, the difference between the two groups was marginally significant ($p \leq 0.086$) in favor of vehicle.

Safety analysis of Study 04 shows that percentage of patients with one or more adverse events in the Diclofenac group (81%) was similar to that in the vehicle group (87%) with p=0.42. The most frequently reported dermal adverse events were: pruritus, rash, dry skin and application site reactions. The Diclofenac patients had a numerically higher incidence of rash, dry skin, and application site reactions than their respective control groups ($p>0.075$). The incidence of pruritus was statistically significantly higher (p=0.001) in the vehicle patients (59%) than in the Diclofenac patients (36%).

Safety analysis of Study 07 shows that percentage of patients with one or more adverse events in the Diclofenac group (93%) was numerically greater than that in the vehicle group (82%) with p=0.14. Statistically significantly more Diclofenac patients (N=51, 91%) reported dermal adverse events compared to 41 patients (75%) in the vehicle group (p=0.039). Statistically significantly more patients in the Diclofenac group reported application skin reaction (p=0.043), including contact dermatitis ($p<0.0001$) and rash (p=0.001).

Integrated Safety Analysis (Studies 03, 04, and 07 combined)

Of the 423 patients evaluable for safety in the three Phase 3 studies 03, 04, and 07, there were 211 Diclofenac treated patients and 212 vehicle treated patients. Of them, 183 (87%) Diclofenac patients and 178 (84%) vehicle patients experienced one or more adverse events during the study (p=0.4). There was a statistically significant difference between treatment groups in favor of vehicle relative to the number of patients with treatment interrupted due to adverse events (9% vs. 2%, p=0.005), number of patients discontinued (18% vs. 4%, p=0.001), number of patients with related adverse events (81% vs. 72%, p=0.04), and the number of patients with no action taken (p=0.03). Numerically more Diclofenac patients (172, 82%) had skin adverse events than vehicle patients (160, 75%) with p=0.1. There was a statistically significant difference (Table 17) between treatment groups relative to the following skin adverse events: contact dermatitis (22% vs. 3%, p=0.001), dry skin (23% vs. 14%, p=0.02), scaling (16% vs. 8%, p=0.02), and rash (39% vs. 18%, p=0.001).

OVERALL REVIEWER'S CONCLUSIONS (which may be conveyed to the sponsor):

Primary efficacy analysis in each of the pivotal Studies CT-1101-03 and CT-1101-04 showed that relative to the primary efficacy variable, proportion of patients with "Complete Clearance" status as measured by CLNS=0 at the Follow-Up visit, Diclofenac gel was statistically significantly better ($p<0.016$) than vehicle in the treatment of patients with actinic keratosis. Primary efficacy analysis of the supporting, single-center, Phase 3 Study CT-1101-07 showed that Diclofenac gel was only marginally better (p=0.061) than vehicle in the treatment of patients with actinic keratosis. Secondary efficacy analysis in each of the three Phase 3 studies supported the claim that Diclofenac gel was statistically significantly better ($p<0.009$) than vehicle in the treatment of patients with actinic keratosis.

Integrated primary efficacy subgroup analysis of the three Phase 3 studies combined showed that Diclofenac gel was statistically significantly better than vehicle in each of the age groups ($p<0.0036$), in males ($p<0.0001$), and in the major anatomic region including forehead, central face, scalp, and neck ($p<0.0001$). Integrated primary efficacy subgroup analysis showed that Diclofenac gel was only numerically better than vehicle in the major anatomic region including back of hand and arm/forearm ($p=0.37$) and Diclofenac was only marginally significantly better than vehicle in females ($p=0.063$). This reviewer recommends

[ ]

The integrated safety analysis of Studies CT-1101-03, CT-1101-04, and CT-1101-07 showed that there was no statistically significant difference between the two treatments relative to the percentage of patients with one or more adverse events ($p=0.4$). However, the integrated safety analysis showed that Diclofenac gel was statistically significantly worse than vehicle relative to the number of patients with treatment interrupted due to adverse events ($p=0.005$), number of patients discontinued ($p=0.001$), number patients with related adverse events ($p=0.04$), and number of patients with no action taken ($p=0.03$). Numerically more Diclofenac patients (172, 82%) had skin adverse events than vehicle patients (160, 75%) with $p=0.1$. Diclofenac gel was statistically significantly worse than vehicle relative to the number of patients with the following skin adverse events: contact dermatitis (22% vs. 3%, $p=0.001$), dry skin (23% vs. 14%, $p=0.02$), scaling (16% vs. 8%, $p=0.02$), and rash (39% vs. 18%, $p=0.001$). This is a matter of the clinical judgement of the reviewing medical division to decide whether Diclofenac gel should be approved given the safety issues described above.

/S/ 06.02.99

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics III

/S/ 06/07/99

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, Biometrics III

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-005
HFD-540
HFD-540/Mr. White
HFD-540/Dr. Wilkin
HFD-540/Dr. Ko
HFD-725/Dr. Huque
HFD-725/Dr. Srinivasan
HFD-725/Dr. Freidlin
HFD-344/Dr. Carreras
Chron. (HFD-725)
This review contains 22 pages.
wordfile\solarase\21005_r2\05-26-99