Number of Patients with New Lesions

	Day 30	Day 60	Day 90	30-d FU
Diclofenac	6	5	7	6
Vehicle	10	12	14	14

IGII And PGII Parametric Analysis at 30-d Follow-up Visit (Mean Score)

		Day 30	Day 60	Day 90	30-d Follow-up
IGII*	Diclofenac	0.7	1.1	2.1	2.7
	Vehicle	1.0	1.5	1.7	1.9
	p-value	0.144	0.184	0.192	0.009
PGII	Diclofenac	1.0	1.2	1.9	2.2
	Vehicle	1.1	1.4	1.4	2.8
	p-value	0.842	0.551	0.112	0.119

*IGII=Investigator's global improvement index; PGII=Patient's global improvement index.

Distribution of IGII and PGII Scores

	Score	4	3	2	1	0	-1	-2	Total
IGII* Day 30	Diclofenac	0	1	5	16	11	3	1	37
	Vehicle	0	6	11	12	17	3	0	49
Day 60	Diclofenac	1	5	4	11	3	2	0	26
	Vehicle	0	12	12	8	10	3	0	45
Day 90	Diclofenac	9	9	8	7	6	1	0	40
	Vehicle	7	13	7	11	11	4	0	53
30-d FU	Diclofenac	16	20	4	3	4	0	0	47
	Vehicle	9	14	9	5	10	3	0	50
PGII* Day 30	Diclofenac	0	4	12	8	8	1	3	36
	Vehicle	0	8	9	11	19	1	0	48
Day 60	Diclofenac	1	4	13	9	7	1	2	37
	Vehicle	1	11	10	12	15	0	0	49
Day 90	Diclofenac	7	11	8	11	2	3	1	43
	Vehicle	3	14	7	14	12	4	0	54
30-d FU	Diclofenac	10	14	13	7	6	2	0	52
	Vehicle	3	17	12	8	14	0	0	54

*IGII=Investigator's global improvement index; PGII=Patient's global improvement index; FU=follow-up; Scores: 4=completely improved, 3=significantly improved, 2=moderately improved, 1=slightly improved, 0=no change, -1=slightly worse and -2=significantly worse

Comments

1. Baseline target lesion scores were higher in the diclofenac group than in the vehicle group (see above). This difference was partially controlled for in the analysis of lesion counts by using the change from baseline as the test variable. However, for the analysis of the proportion of patients completely cleared of lesions, covariates were not used and the treatment contrast might be biased favoring the Vehicle group.
2. It is evident from the data that the vehicle group also experienced improvement. It is not clear how much this was due to the ancillary measures or whether the vehicle had a beneficial effect above no therapy. This study shows that at the 30-day post-treatment follow-up visit, 13/50 patients given vehicle had no change or worsening; thus 74% of vehicle-treated patients had improvement, and the mean change in CLNS was 4.8, with a baseline count of 8.0 in that group (-60%). The spontaneous rate for regression of AK lesions has been reported to be as high as 26% in 36% of patients in 12 months (Marks *et al* Br J Dermatol 115:649, 1986).
3. There is some discrepancy between IGII and PGII for "completely improved". The Applicant explains this as due to difference in the interpretation by physician and patient of "clearing", as some discoloration might have been perceived by patients

"significantly improved" but not "completely improved". Such difference may also account for the discrepancy between the patient evaluations and the more objective CLNS=0:

	Diclofenac	Vehicle
CLNS=0	34%	18%
IGII=0	34%	18%
PGII=0	19%	6%

Lesion Counts by Major Body Areas (Treatment "Blocks")

This was an exploratory analysis of TLNS (not CLNS) using actual data (not LOCF) by the Applicant, as shown in the following Table.

TLNS by Major Body Area

	Diclofenac		Vehicle	
	Baseline (Mean)	30-d Follow-up (Mean)	Baseline (Mean)	30-d Follow-up (Mean)
MBA	N=56	N=47	N=55	N=51
Forehead	9.2	1.4 (-85%)	7.9	2.6 (-67%)
Central Face	10.7	0.2 (-98%)	8.8	2.1 (-76%)
Scalp	11.2	1.6 (-86%)	8.8	3.5 (-81%)
Back of Hand	9.0	3.9 (-57%)	8.0	4.0 (-50%)
Arm	6.1	0.6 (-90%)	7.2	1.0 (-86%)

TLNS=target lesion number score

Comment The data indicate that lesions on the forehead and face show the greatest difference between treatment groups. The Applicant submitted an analysis of the data on clearance of lesions by anatomical location upon request:

	Proportion of patients with CLNS=0 at 30 days Post-Treatment Follow-Up (LOCF)		
Location	Diclofenac	Vehicle	p-value
Head/Neck	17/35 (49%)	7/38 (18%)	0.0078
Hand, Arm/Forearm	2/21 (10%)	3/17 (18%)	0.4675

Conclusion: Hyal's diclofenac gel was superior to vehicle in clearing AK lesions in the head and neck regions. Analysis on the clearance of lesions for the hands and for the arms/forearms should be useful information to be reflected in labeling.

8.2.3.4.3 Safety

Exposure

Mean duration of treatment was 64.5 days for the diclofenac and 85.4 days for the vehicle groups. The total dose was 86.7 Gm for the diclofenac and 116.6 Gm for the vehicle groups. The lower exposure to study medication in the diclofenac group was due to the greater number of early terminations.

Adverse Events

Adverse events were reported in 52/56 and 45/55 patients of the diclofenac and vehicle groups, respectively. Their incidence is shown in the Table in Appendix V.

Comment The most common events were application site reactions (ASRs) including contact dermatitis, pruritus, rash, dry skin, exfoliation, pain, and paresthesia. Contact dermatitis and rash were statistically significantly different between treatment groups. All but six dermal adverse events were considered *mild* to *moderate* in intensity and were generally self-limited. Apart from ASRs, the only AEs considered related to treatment were in the diclofenac group: asthenia 1, fever 1, oral ulcer 1, dyspnea 1, sinusitis 1 and conjunctivitis 1.

Serious Adverse Events and Deaths

Six patients experienced serious AEs, all considered *unlikely* to be related to treatment:

- Diclofenac 4: hospitalization for chest pain due to heartburn 1, prostatic cancer 1, hospitalization for kidney infection 1, and SCC 1.
- Vehicle 2: hospitalization for congestive heart failure 1, and SCC 1.

One death occurred (diclofenac gel group) due to cardiopulmonary failure not related to treatment (coronary heart disease, cardiomyopathy, ventricular tachycardia evident in pre-study medical history).

Discontinuation due to Adverse Events

There were 21 patients in the diclofenac and 4 in the vehicle groups who discontinued treatment because of adverse events:

Diclofenac - contact dermatitis 18, pruritus 1, prostate cancer 1, cardiomyopathy 1.
Vehicle – contact dermatitis 1, ASR 1, right heart failure 1, rash/paresthesia 1.

Eczematous Type Reaction Score/Area of Involvement Score (ETRS/AIS)

The distribution of ETRS/AIS (mean number of events) is shown in the following Table.

	Diclofenac			Vehicle		
MBA	N*	Mean ETRS	Mean AIS	N*	Mean ETRS	Mean AIS
Scalp	1	1.0	2.0	0	0	0
Forehead	9	1.6	2.2	1	0	2.0
Central face	4	1.3	2.0	1	1.0	2.0
Back of hand	7	1.4	2.0	0	0	0
Arm	6	1.7	2.4	0	0	0
Total	27			2		

*N=number of patients experiencing ETR

Comment More reactions were reported in the diclofenac-treated group. The scalp appears to be least likely to be affected (similar to CT1101-03). Mean ETRS for each treatment "block" was between 1 and 2, and correlated with *definite erythema* to *erythema and induration*. The AIS indicated that most reactions were localized to the treatment "block" although there was a tendency to spread beyond the site on the forehead and on the arm.

Provocative Use Test (PUT)

Data have not been presented in this report on PUT. A separate report on PUT given by the Applicant has been reviewed and is discussed in Section 10.4.3.2.9.

Clinical Laboratory Tests

There were no consistent clinically significant abnormalities detected in the following tests: CBC, serum chemistry and urinalysis.

Antibodies to Diclofenac

Fifty-three (53) of 56 diclofenac-treated patients had blood drawn after cessation of treatment for analysis for ADA. Evidence of sensitization to diclofenac was not detected.

Serum Diclofenac Levels

Serum diclofenac levels were measured in 52 of the 53 diclofenac-treated patients including 7 who participated in PUT. The majority of samples resulted in values below detection level - ng/ml) while the remainder ranged between 7 and 30 ng/ml, much

lower than typical peak diclofenac levels associated with therapeutic dosing *per os* for symptomatic control of arthritic conditions. Post-treatment samples did not detect diclofenac beyond the eighth day of discontinuation.

8.2.3.5 Conclusions

1) In patients treated with a 90-day regimen using 0.5 g bid per 5cm x 5cm application block, clearing of AK lesions by Hyal's topical diclofenac gel was not statistically significant when compared to vehicle gel. Although there was a positive treatment effect from diclofenac, patients treated with vehicle also had considerable improvement, thus making results of this study not conclusive.
2) Diclofenac gel was generally well tolerated, with mild to moderate application site reactions being the most prevalent adverse events reported.
3) No evidence of systemic allergic sensitization to diclofenac was demonstrated in this study.

8.2.4 Trial #4. A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of CT1101 in the Treatment of Actinic Keratoses (CT-1101-01) [Conducted 10/13/94 to 6/25/95]

8.2.4.1 Objective

To compare the efficacy and safety of topically applied 3% diclofenac in — hyaluronan gel (Hyal-CT-1101) to that of the — hyaluronan gel vehicle alone in the treatment of AK.

8.2.4.2 Design Phase 2, randomized, placebo-controlled, double-blind, parallel-group multi-center trial to study the efficacy and safety of 3% diclofenac gel in the treatment of AK for up to 12 weeks (see schema under section 8.2.4.3.1), with 3 Investigators and 160 subjects planned to be in 2 arms (active vs vehicle).

Comment This early phase study has a protocol which forms the prototype of the phase 3 trials. A discussion of the differences in design is in Section 9.2.

8.2.4.3 Protocol Overview

8.2.4.3.1 Population and Procedures

A sample size of 160 was planned. All participants were outpatients/new patients initially seen by the investigators or designates. Selection criteria were:

INCLUSION: Male or female, aged 18 or older, with AK on head, neck, hands or arms

EXCLUSION

- Sensitivity to or asthma associated with use of NSAID, and/or any contraindications to treatment with ASA or NSAID
- Significant concurrent illness including peptic ulcer, liver, renal or heart disease
- Use of concomitant drugs that might interfere with evaluation, including systemic corticosteroids, antineoplastic drugs, etretinate, isotretinoin and vitamin A
- Lactation or pregnancy
- Significant abnormal liver or renal function test or CBC
- Skin condition that might confound study, including Bowen's disease, basal cell carcinoma or SCC
- Use of investigational drug or involvement in clinical study within 3 months of entry
- Unwillingness to discontinue use of cosmetics that might have interfered with study medication

- Worked outdoors or deliberate exposure of skin to sun or UV light

Withdrawal could be due to patient request, adverse experience, non-attendance, protocol violation, worsening or death.

Eligible patients were randomized in a 1:1 ratio to active diclofenac gel or vehicle. The study consisted of three phases: screening, treatment and follow-up, as shown in the following schema:

Procedure	Baseline	Wk 4	Wk 8	Wk 12	End of Therapy[1]	Follow Up[2]	Post-Termination Follow-up[3]
Demographics	x						
Enrollment criteria	x						
Medical history/physical exam	x						
Lesion count	x	x	x	x			x
Lesion quality assessment							
3-point baseline score	x						
5-point schedule score		x	x	x	x		
4-point follow-up score						x	
4-point post-termination FU score							x
Photography	x	x	x	x		x	
Hematology/biochemistry	x				x		
Concomitant medications (incl sunscreens)	x	x	x	x		x	x
Drug accountability	x				x		
Adverse Events		x	x	x			
termination record				x			

1=Resolution of lesions before week 12 resulted in cessation of therapy. However, the end-of-therapy assessment had to be conducted.
2=All assessments after cessation of therapy due to resolution of lesions (up to & including week 12 visit) were "follow-up" assessments.
3=4 weeks after week 12 assessment irrespective of resolution before week 12.

The study medication lot number was UMD3 for the active and VBE3 for the placebo gel (these lots containing hyaluronic acid [HA] from ———— ; HA in test drugs for phase 3 and for proposed marketing is from ————————). The gel was expressed from the tube for each dose, estimated to be of the size of a pea. This was applied to study area and rubbed in. The estimated quantity was 0.25 Gm of gel per site (5 cm x 5 cm) twice a day. Treatment lasted 12 weeks unless lesions were cleared. Prohibited concomitant treatments were: systemic corticosteroids, antineoplastic drugs, etretinate, isotretinoin and vitamin A. Use of sunscreens was recorded.

Comment This study used a smaller dose (0.25 Gm per 5 cm x 5 cm area bid) than that proposed in the labeling (0.5 Gm per 5 cm x 5 cm area bid).

8.2.4.3.2 Evaluability Criteria See section 8.2.4.3.5 re: per-protocol analysis.

8.2.4.3.3 Endpoints

Efficacy Parameters

At baseline, lesions were assessed on a 3-point scale:
mild=lesions clearly visible, thin but palpable scales; moderate=lesions clearly visible and palpable, slightly thickened scales; severe=thick, hyperkeratotic and/or florid lesions with palpable, well defined borders.

in addition to lesion counting, the following post-baseline global improvement assessments were made -

1. Scheduled visit assessment: 5-point scale:
- no change
- some lesions cleared with some scales decreased in thickness; many remained the same
- many lesions cleared; scales decreased in thickness
- majority of lesions barely palpable
- lesions cleared but slight redness allowed

2. Follow-up visit (after clearing) assesment: 4-point scale:
- treated area continuing to improve
- lesions beginning to reappear
- moderately severe lesions reappeared
- very severe lesions reappeared

3. Termination visit (week 16) assessment: 4-point scale:
- no change
- remaining lesions resolved
- improving but lesions not totally resolved
- lesions reappeared since treatment ended

Comment The use of different scales at different times makes it difficult to analyze the global data. Comparison to baseline requires reliance on an Investigator's memory and is inherently less objective than the use of static scales.

Safety Parameters
AEs/serious AEs, hematology, biochemistry
pregnancy test at baseline for premenopausal women

8.2.4.3.4 Statistical Considerations

The primary population for efficacy and safety analyses was the intent-to-treat group. A per protocol analysis was performed which excluded protocol violators including prohibited medication users and non-compliant users of test medication (<0.25 Gm per dose average).

"The primary analysis was based upon lesion counts. The analyses were performed on both data presented as (a) actual counts and (b) percent changes from baseline. Because there was a very evident distribution problem with the data, distribution free methods were chosen." SAS NPA1WAY was used as the univariate test without consideration of other possible factors implicated in treatment outcome. This method ranks the data and performs an ANOVA on the ranked data providing a Wilcoxon score." To address multiplicity because of analysis being done twice (end of treatment and post-termination follow up), Bonferroni's adjustment was made for the lesion count and percent difference contrasts, via a bootstrap analysis.

Covariates were tested with NPAR1WAY for their impact on lesion counts and were included in the multivariate analysis model for the following factors: age (cutoff at 70), sex, baseline severity (mild, moderate, severe), location (head & neck, hands, arms), compliance (use of 0.25 Gm per dose/<0.25 Gm per dose) and investigator. Sunscreen was not included because of sporadic and episodic use.

Sample size estimation was based on a change of 1.8 or more lesions and S.D. of 4 (Thompson *et al.* N Engl J Med 329:1147, 1993). With an α error probability of 0.05 and

β error probability of 0.20, 80 patients per treatment group would be required.

Comments

1. The primary analysis should be based on clearing of lesion counts.
2. Sample size calculation was not based on the rate of clearing of lesions, which is the preferred primary variable.
3. In the original protocol, the time point for primary analysis was not stated. The study report summary states: "Initially, the primary efficacy parameter was to be end of treatment lesion counts assuming that all effects to be demonstrated by the topical treatment would be accrued by that time (12 weeks). However, like several other AK preparations, a more optimal response was identified as occurring at least 30 days after treatment cessation, as evidenced in a previously completed open study at the University of British Columbia in Canada. The primary analysis in this present investigation therefore also includes a post-termination follow-up lesion count. The Applicant has applied multiple comparison with Bonferroni methodology in this study report for lesion counts.

8.2.4.4 Study Results

The Investigators were:

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Fremantle Dermatology Clinic	Unit 21	Private Medical Suites
229 High street	14 Waratah Street	Royal Melbourne Hospital
Fremantle	Mona Vale	Grattan Street
Western Australia	New South Wales	Parkville, Victoria
Australia	Australia	Australia

8.2.4.4.1 Disposition and Demographics

Patient Disposition

	Diclofenac	Vehicle
randomized	74	77
applied treatment	73	77
completed all study visits	50	65
"withdrawals"	24	12
• adverse events	16	3
• protocol violation	2	2
• patient request	2	2
• lost to Follow-up	1	1
• lesions resolved	3	3

Baseline Demographics

		Diclofenac	Vehicle
Age	mean ± SD	67.5 ± 10.3	69.2 ± 10.9
	range	27-87	36-89
Sex	M:F	49:24	40:37
BLC*	mean ± SD	9.8 ± 6.6	11.3 ± 7.7
	range	1-40	1-40
BLS**	mild	27	16
	moderate	36	45
	severe	10	16
Treatment lesion distribution	Head and neck	45	46
	Hands	23	25
	Arms	5	6

*BLC=baseline lesion counts; **BLS=baseline lesion severity; no significant differences between arms for any parameter (p>0.05).

Comment The racial composition of the study sample has not been given. The demographic data given above indicate that the two treatment arms were comparable.

8.2.4.4.2 Efficacy

Primary Efficacy Variable

The primary efficacy variable for this review is the proportion of patients showing complete clearing of all lesions at the post-termination follow-up visit.

Proportion Of Patients Experiencing Complete Clearance At Post-Termination Follow-Up*

	Proportion	*p* value
Diclofenac	17/45 (38%)	
Vehicle	4/42 (10%)	0.002

*4 weeks after week 12 assessment (irrespective of resolution before week 12) in subjects without further treatment

In the 31 patients (21 active, 10 placebo) who had clearing by the end of treatment, time to complete resolution was 72 (S.D. 25) days for active and 78 (S.D. 22) days for placebo groups. This difference was not significant by the *t* test. Analysis was not further performed with additional patients who cleared by post-termination follow-up visit.

Comments

1. The above data using ITT analysis do not include all patients but only those who came to the post-termination visit without further treatment. Analysis at the end of treatment (day 84) used the entire randomized population except one subject (randomized to active, dropped after initial visit without treatment), and showed the rates of clearing were 21/73 for diclofenac and 10/77 for vehicle (p=0.029).
2. The lesion count analyses were adjusted using Bonferroni methodology. The comparisons for clearing were not adjusted for multiplicity. However, in view of the robustness of these data, inclusion of an adjustment is likely to affect the conclusions to be drawn.

Secondary Efficacy Variables

This study used the following parameters for primary endpoints: lesion count changes and percent changes in lesion counts from baseline at end of treatment and at post-termination follow-up. For this review, they are treated as secondary variables.

Lesion Count Changes and Percent Lesion Count Changes

			Baseline (mean)	Delta Baseline: End of Treatment (mean)	Delta Baseline: Post-Termination FU* (mean)
Lesion counts	Diclofenac	N=73	9.8	5.5	6.2
	Vehicle	N=77	11.3	4.7	2.4
	p-values**			0.293 (1.000)	0.0009 (0.023)
Percent changes	Diclofenac	N=73		42.5	56.1
	Vehicle	N=77		29.5	23.6
	p-values			0.047 (0.714)	0.0001 (0.023)

*FU=follow-up; **p-values by Wilcoxon rank sum test, with adjusted p values (Bonferroni) in parentheses.

Global assessments at the interim visits and at post-termination follow-up were presented with actual data, and not using intent-to-treat methodology with last observation carried forward. These will not be discussed here.

Comment The vehicle group also experienced further improvement. It is not clear how much this was due to the ancillary measures or whether the vehicle had a beneficial effect above no therapy. This study shows that at the end of treatment, 40/63 patients given vehicle had no change or worsening; thus over 1/3 of the vehicle group had improvement and the mean change in lesion counts was -4.7 (-30%). This is consistent with the spontaneous rate for regression of AK lesions observed by Marks *et al* (26% in 36% of patients in 12 months). The study report attributes the placebo effect to a combination of the gel's hydrating properties, to the natural regression of AK lesions, and to "an actual therapeutic effect of the vehicle." The hydrating effect is expected to wane upon cessation of treatment. The Applicant concedes that the "therapeutic effect" of hyaluronan is speculative, but the benzyl alcohol in the vehicle can be irritating, and thus "immunologically provoking" to the skin. These hypotheses remain to be substantiated.

Known "recurrence" occurred in 9/21 (43%) of active treatment patients who had complete resolution at the end of treatment, and in 7/10 (70%) of such placebo patients. Mean time to recurrence from termination was 93 (S.D. 34) days for the active group and 62 (S.D. 30) days for the placebo group (p=0.074).

Comment It is not clear whether the "recurrences" were from sites of previous lesions or were new lesions; exact mapping was not actually done in this study (see also discussion in Section 9.4.

Per protocol analysis of lesion count changes and percent changes from baseline corroborated the findings using ITT analysis.

Lesion Counts by Major Body Area

Changes in Lesions by Major Body Area

	Diclofenac		Vehicle	
	E-O-Tr (Mean)	Post-Term* Follow-up (Mean)	E-O-Tr (Mean)	Post-Term* Follow-up (Mean)
Location	N=73	N=45	N=77	N=42
Head & neck	-6.3 (-53.8%)	-7.5 (-63.9%)	-5.2 (-38.2%)	-3.2 (-31.7%)
Hands	-4.2 (-21.2%)	-3.4 (-31.1%)	-4.8 (-21.8%)	-1.2 (-5.5%)
Arms	-3.6 (-38.1%)	-6.0 (-100.0%)	0.7 (5.0%)	-2.2 (-36.7%)

*E-O-Tr=end-of-treatment; Post-Term=post-termination (4 weeks after week 12 in subjects without further treatment); data shown as changes from baseline.

Comment Baseline values have not been given. Post-treatment data have not been analyzed with ITT population. Between-group p-values for each location have not been provided. Despite these, it seems reasonable to conclude that the hands showed the least changes by the time of the post-termination follow-up.

Additional Comment on Efficacy Data There was a significant center effect on the efficacy data, as site 1 (Dr. Gebauer) had higher baseline lesion counts. The study report attributes the difference as due to Dr. Gebauer relying more heavily on tactile identification and qualification of lesions. This center also had greater reduction in lesion counts than in other centers. However, the positive trend of active over vehicle is seen throughout the three centers.

8.2.4.4.3 Safety

Exposure

Mean duration of treatment was 73.8 days for the diclofenac and 77.4 days for the vehicle groups. The average dose was 0.67 Gm/d for the diclofenac and 0.70 Gm/d for the vehicle groups (total dose 49 Gm and 54 Gm respectively). The slightly lower

exposure in the diclofenac group was due to the greater number of early terminations.

Adverse Events

Adverse events were reported in 31/73 and 21/77 of patients in the diclofenac and vehicle treatment groups, respectively. See Appendix I for AE incidence Table.

Comments

1. The only AEs considered related to treatment were those in the Skin and Appendages category. Among those categorized under Skin and Appendages, the following were considered unlikely as being related - bursitis (placebo 1), adenocarcinoma (placebo 1), edema (placebo 1), herpes zoster (placebo 1), infection (placebo 1), melanoma (active 1, placebo 1) and surgical procedure (placebo 1).
2. The definition of "application site reaction" (ASR) in this study has not been provided.

Serious Adverse Events

Five patients experienced serious AEs, all considered *unlikely* to be related to treatment:

- Diclofenac 2: melanoma 1, sinus bradycardia 1.
- Vehicle 3: skin adenocarcinoma (primary unknown) 1, hospitalization for skin graft for sun damage on dorsum of hand 1, & melanoma 1.

Discontinuation due to AEs There were 16 patients in the diclofenac and 3 in the vehicle group who discontinued treatment because of adverse events:

Diclofenac	Vehicle
#067 dry skin/pruritus/ASR/localized edema	#029 adenocarcinoma
#074 paresthesia	#119 ASR
#080 rash/pruritus/localized edema	#106 bursitis/edema
#094 rash/ASR/localized edema	
#099 rash/pruritus/localized edema	
#102 rash/ASR	
#105 pruritus/paresthesia/ASR	
#114 ASR	
#116 dry skin	
#123 dry skin/pruritus/ASR	
#077 rash/pruritus/localized edema	
#110 rash/pruritus/paresthesia/ASR	
#111 paresthesia/ASR	
#150 rash/pruritus	
#176 sick sinus syndrome	
#131 rash/dry skin/ASR	

Clinical Laboratory Tests

No consistent clinically significant abnormalities detected (CBC and serum chemistry)

8.2.4.5 Conclusions

1) In patients treated with an 84-day regimen of 0.25 Gm bid to a 5 cm x 5 cm application "block", topical diclofenac gel was superior to vehicle in the treatment of AK lesions.

2) Diclofenac gel was generally well tolerated, with rash, pruritus, dry skin and application site reaction being the most prevalent AEs reported.

3) This study used a smaller dose (0.25 Gm/5 cm x 5 cm) than that proposed in the labeling (0.5 Gm/5 cm x 5 cm) but nevertheless demonstrated effectiveness for the

intended use. It lends further support to the data obtained in phase 3 trials.

8.2.5 Trial #5. A Randomized, Double-Blind, Placebo-Controlled Evaluation of Topical Hyaluronic Acid/Diclofenac in the Treatment of Solar Keratoses (PMCI 93/23 AK-CT1101-02; ST-5101-AUS-01) [Conducted 9/27/94 – 7/8/96]

8.2.5.1 Objective To compare the safety and efficacy of topically applied 3% diclofenac in — hyaluronan gel to that of the gel vehicle in the treatment of actinic keratosis.

8.2.5.2 Design Phase 2, randomized, placebo-controlled, single-center, double-blind, parallel-group trial to study the efficacy and safety of 3% diclofenac gel in the treatment of AK, with one Investigator and two arms (active vs vehicle).

Comment Although this trial was well-controlled, it was a single-center study and will not be considered "adequate" for the purpose of this review. It lends supportive data and additional evidence of safety. For comparison with the design of phase 3 trials, see Section 9.2.

8.2.5.3 Protocol Overview

8.2.5.3.1 Population and Procedures

A sample size of 130 was planned. All participants were outpatients of the Dermatology Clinic of the Peter MacCallum Cancer Institute (PMCI), who were aged 21 or over, with a conspicuous AK lesion and were mentally competent. Females were post-menopausal, sterilized or taking adequate contraceptive measures. Exclusion criteria:

- under 21 years of age
- not given signed informed consent
- mentally incompetent
- use of confounding drugs, specifically systemic corticosteroids, systemic retinoids, antineoplastics or cyclosporine (NSAIDs initially disallowed; this criterion removed before recruitment began)
- current participation in another drug or device study; previous participation in drug study required elapse of 5x half lives of the drugs since last intake
- known sensitivity to NSAIDs or — sunscreen preparations
- abnormal lab test results, including hematology, urea, electrolytes and liver function

Treatment could be discontinued because of consent withdrawal, clearing of the target AK lesion, worsening, poor compliance or serious adverse reaction.

Eligible patients were randomized in a 1:1 ratio to active diclofenac gel or vehicle. The study was conducted according to the following schema:

Procedure	Baseline[1]	Wk 8	Wk 16	Wk 24	End of Therapy[2]
Demographics	x				
Medical history	x				
Site of keratosis	x				
Lesion measurement	x	x	x	x	
Appearance of keratosis*	x				
5-point schedule score		x	x	x	
Photography	x	x	x	x	
Hematology/biochemistry	x				x
Concomitant medications	x	x	x	x	
Drug accountability	x				x
Adverse Events		x	x	x	
Termination record					x

1=randomization to treatment occurred one week after baseline enrollment, when lab test results were available.
2=end-of-therapy assessment had to be conducted whenever patient ceased treatment, in addition to the scheduled assessments.
*scaliness, thickness, inflammation and ulceration, to be used for prognostic analyses of efficacy data

The study medication lot numbers were ULD2 and VGD6 for the active and ULE2 and WCE7 for the placebo gels (gels containing HA from ————). Study gel was applied to target lesion and rubbed in twice daily for 24 weeks or sooner if the AK lesion cleared. The volume was measured using an applicator fitting tightly onto the end of the medication tubes. However, the Investigator reported that too large a quantity was drawn up with the applicator, and from 11/23/94, the applicator was no longer used. The protocol did not specify the amount to be applied.

All patients were given ———— 15+ (sunscreen cream ———— ———— to be applied to the target treatment area not less than 5 minutes after morning application of the study gel. They might also apply the sunscreen to other lesions. Drugs for unrelated diseases were allowed and recorded.

Compliance Compliance was estimated by weighing of the medication tubes but could not be assured because the protocol did not specify the amount of medication to be applied each time.

8.2.5.3.2 Evaluability Criteria Not applicable; no per protocol analysis planned

8.2.5.3.3 Endpoints

Efficacy Parameters

1. Quantitative lesion response. Diameters of the target AK lesions were measured.
2. Semi-quantitative lesion response. This was a 5-point scale on improvement of the target AK lesion: 1=lesion not evident/complete resolution, 2=great improvement, partial resolution, 3=slight improvement, minimal response, 4=no change, and 5=worse.
3. Photography. The Investigator was also to use the above 5-point scale to grade lesion improvement on photographs. This was found to be inaccurate due to variations in lighting, position, and scale. Photographs were retained for record but not used.

The primary variable was to be the rate of complete resolution of the target AK lesion.

Safety Parameters
AEs/serious AEs, hematology, biochemistry

8.2.5.3.4 Statistical Considerations

The primary population for efficacy and safety analyses was the intent-to-treat group.

The primary endpoint was complete resolution, and its rate was to be compared between the two treatment arms with Fisher's exact test. The response data (5-point scale) were compared with Wilcoxon rank sum test. The study report also provided univariate analysis of possible prognostic factors on outcome: scaliness, thickness, inflammation, ulceration, site and size of lesions.

Comment The time point of primary analysis was not specified in the protocol. In the study report, it is stated: "The primary measure of efficacy was the clinical resolution of the target lesion at the time the patient ceased treatment."

Safety data were analyzed with Fisher's exact test for adverse event rates. Laboratory tests were summarized for the baseline and end of treatment results, with abnormal results listed.

Sample size estimation was based on the expected rate of lesion resolution with the use of sunscreen; it was assumed that the rate of complete resolution in the vehicle arm would be 25%. With 65 per arm, there would be a power of 80% to show the complete response rate in the active arm to be 50% (2-sided alpha of 0.05).

8.2.5.4 Study Results

The Investigator was: Lena McEwan, MB BS, FRCS (Eng), FRACS
Sessional Consultant, Skin Unit
Peter MacCallum Cancer Institute
481 Little Lonsdale Street
Melbourne, Victoria, Australia 3001

8.2.5.4.1 Disposition and Demographics

Patient Disposition

	Diclofenac	Vehicle
randomized	65	65
completed all study visits	36	49
"withdrawals"	29	16
• adverse events	13	3
• poor compliance	1	2
• withdrew consent	2	3
• lost to follow-up	1	0
• complete response	10	7
• lesion worse	1	0
• "intercurrent illness"	1	1

The study report gave two listed as "other" under diclofenac: lesion became irritable (#099), and did not return for assessment (#013). These have been reclassified under "adverse event" and "lost to follow-up" here.

Comment Two patients were discontinued on the basis of "intercurrent illness". These should have been reclassified as "adverse events". One patient in the active group had the "intercurrent illness" as local and generalized rash (believed to be due to Renitec®) and one in the placebo group as Colle's fracture of right wrist.

Baseline Demographics

		Diclofenac	Vehicle
Age	median	70	72
	range	48-77	48-87
Sex	M:F	39:26	34:31
Target lesion	median diameter (mm) 12-6 o'clock	20	20
	median diameter (mm) 3-9 o'clock	18	18
	≤400 sq mm	35 (55%)	31 (48%)
	>400 sq mm	29 (45%)	34 (52%)
Target lesion distribution	Head and neck	29	30
	Hand	8	20
	Arm	28	14
	Lower leg/knee	0	1

Comment The treatment arms were comparable, except that there were more target lesions on the hands and fewer on the arms in the placebo group. However, the head/neck and non-head/neck distribution was similar between the treatment groups.

8.2.5.4.2 Efficacy

Primary Efficacy Variable

The primary efficacy variable is the proportion of patients showing complete clearing of target lesions at treatment cessation.

Proportion Of Patients with Complete Lesion Resolution At End of Treatment

	Proportion	95% C.I. for Resolution Rate	p-Value*
Diclofenac	19/65 (29%)	19%-42%	
Vehicle	11/65 (17%)	9%-28%	0.140

*Fisher's exact test; the estimated *difference* in resolution rate is 12% (95% CI=5%-29%)

Comments

1. Although the proportion for complete clearing favors diclofenac numerically, this trial falls short of demonstrating statistical significance because of considerable vehicle effect.
2. Data from other studies indicate that the difference between diclofenac and vehicle in the rate of complete resolution occurred primarily after the treatment period. This study does not include an assessment post-termination.
3. As lesions in the hands and arms may be more difficult to resolve, the choice of lesions in this study, together with the time point for final assessment for efficacy, may be responsible for the failure to demonstrate statistical superiority by the active treatment.

Secondary Efficacy Variable

Clinical Assessment of Lesions at Treatment Cessation

	Active*	Placebo
1=lesion not evident/complete resolution	19 (29%)	11 (17%)
2=great improvement, partial resolution	25 (38%)	29 (45%)
3=slight improvement, minimal response	20 (15%)	15 (23%)
4=no change	3 (5%)	9 (14%)
5=worse	3 (5%)	0
Not assessable**	5 (8%)	1 (2%)

* P value for distribution=0.079 (Wilcoxon rank sum test); **Unassessable patients – active arm: not returned for assessment 2, rash obscuring assessment 3; placebo arm: withdrawn from trial 1.

Comments

1. The analysis should have included the non-assessable patients with last observation carried forward.
2. It is evident from the data that the vehicle group also experienced improvement. It is not clear how much this was due to the ancillary measures (e.g., sunscreen use) or whether the vehicle had a beneficial effect above no therapy.

The Applicant also analyzed the response in relation to prognostic factors including scaliness, thickness, inflammation, ulceration, site and size of lesions. However, the analyses were with pooled data (active + treatment groups together), and were therefore unhelpful in showing the treatment effect of diclofenac.

8.2.5.4.3 Safety

Exposure

Median duration of treatment was 146 days [redacted] for the diclofenac and 168 days [redacted] for the vehicle group. The median number of applications was 256 [redacted], for the diclofenac and 332 [redacted], for the vehicle group. The total weight of gel used was 44 Gm [redacted] for the diclofenac group and 79 Gm [redacted] for the vehicle group. The lower exposure to study medication in the diclofenac group was likely due to the greater number of early terminations (complete resolution or adverse event).

Adverse Events

An adverse event Table with listings according to body systems has not been presented. Instead, the study report lists the adverse events as reported by the Investigator and in the patient diaries. The only analysis is for the clinician's assessment, given in Table 20 of the report as follows:

	Active N=62* N (%)	Placebo N=64* N (%)
Any Adverse Local Reaction	18 (29%)**	3 (5%)
Any Adverse Systemic Reaction	1 (2%)	1 (2%)

*3 in the active group and 1 in the placebo group were excluded as "unknown, no assessments"; **p=0.0002.

Comments

1. The most common adverse events were local dermal reactions in the area of gel application: rash, pruritus, dry skin and edema. However, their incidences have not been given in the report.
2. The AEs could be more appropriately tabulated (1) as incidence (number and percent) under body systems and (2) with respect to severity as separate Tables. "Intercurrent illness" could have been included as adverse events in the Tables and the

Investigator's consideration for relationship to treatment provided. This Reviewer has analyzed the AEs from data listings on Investigator reports and patient diary reports (Tables 18 and 19 of the study report) and their incidences are shown in Appendix II of this review. The figures differ from those in the above Table, as the study report analysis shown above only included information from Investigator reports.

Serious Adverse Events

Four patients experienced serious AE, all considered unrelated to treatment and continued the study medications:

- Diclofenac 2: hospitalization for re-excision of recurrent multifocal basal cell carcinoma 1, follicular mixed cell lymphoma 1.
- Vehicle 2: angina 2.

Discontinuation due to Adverse Events

There were 15 patients in the diclofenac and 2 in the vehicle group who discontinued treatment because of adverse events:

Diclofenac	Vehicle
#006 skin cracking and bleeding	#094 rash
#010 increased redness and scaliness	#049 irritation and stinging
#011 crusty rash	
#016 rash	
#023 irritation and rash	
#035 severe irritation	
#073 rash	
#081 rash	
#096 rash, irritation	
#099 irritation	
#058 rash	
#101 rash	
#116 rash	
#126 rash	
#107 rash (attributed to Renitec®)	

Comment This account given in the study report text (vol 1.82 p.21) is inconsistent with the data in its Table 2 "Account of Patients". Some of the adverse events are not accounted for, e.g., active patients #068, 124, 055 and 056; placebo patients #020 and 102. In addition, some of the patients listed above as being withdrawn due to adverse events were classified under other reasoning in Table 2: complete response for #011 and 016, withdrew consent for #010, intercurrent illness for #107, poor compliance for #023 and "other" for #099. Interestingly, placebo patient #094 who withdrew because of rash was listed twice in Table 2, once under "adverse event" for ***placebo***, and once under "withdrew consent" for ***active***.

Clinical Laboratory Tests

There were no consistent clinically significant abnormalities detected in hematology or serum chemistry.

8.2.5.5 Conclusions

1) This study was not adequately designed, with lack of clear instructions on application of study medication, mandatory concomitant use of a medicated sunscreen, and absence of a proper post-treatment evaluation. These made interpretation of the data very difficult.

2) Superiority of 3% diclofenac over vehicle at the end of treatment was not demonstrated in this study.

3) Diclofenac gel was generally well tolerated, with local skin reactions being the most prevalent adverse events reported.

8.2.6 Trial #6. An Open Study to Assess the Efficacy and Safety of Topical 3% Diclofenac in —— Hyaluronic Acid Gel (HYAL ST5101) in theTreatment of Actinic Keratoses (TDHA-AK-CDN-93-01) [Conducted 2/21/94 to 1/16/95]

Comment This was a single-center, uncontrolled study and cannot be considered as adequate and well-controlled. It was an early exploratory study to determine if 3% diclofenac gel had any efficacy in actinic keratosis. Only a summary of the methodology and findings will be presented in this review.

Design and Methodology of Study This was an open label study enrolling patients aged 18 or older with AK lesions. Patients were to apply 1 Gm of the study medication (3% diclofenac, HYAL ST-5101, synonymous with CT1101; lot number ULD2, containing HA from ———————— , measured with a vaginal applicator, twice daily over the AK lesion(s) and rub in. Treatment lasted up to 210 days, and patients attended a follow-up visit 30 days post-treatment. During the study, visits were at 60 day intervals and consisted of the following measurements:

- Global assessment of lesion response for improvement using the same scale as that of the Investigator Global in CT1101-03 (IGII), but the basis for comparison is not explicitly stated (? baseline)
- Photographic assessment of lesions made by Investigator comparing the two most recent photographs of the target area, using the same scale as the global assessment
- Lesion count added to the protocol for the last 10 patients in this study
- Patient and physician assessment of efficacy and tolerability: rated at the end of study with a 4-point scale: 1=excellent, 2=good, 3=fair and 4=poor
- Clinical laboratory testing (hematology and serum chemistry) at screening and at end-of-treatment
- Provocative Use Testing (PUT) consisting of application of study gel to the left upper inner arm in a dose of 1 Gm bid for 7 days in 5 healthy volunteers and 5 patients who experienced dermal reactions to the gel

Comments
1. This study involved application of 1 Gm of study gel bid (2 times proposed dose in label) and treatment for up to 210 days (proposed duration in label of 60-90 days). Therefore, the efficacy data from this study are not supportive of the intended use conditions for marketing. However, the safety data might be useful, as the drug exposure in this study exceeded the conditions for proposed use.
2. The basis for evaluation of improvement for global assessment is unclear, while photographic assessment compared the two most recent photographs. If the evaluations were based on comparison with different photographs each time, the data would not be comprehensible because of its basing on a moving target. The only solid score would be "cured" or no lesions.

Results

The Investigators were:

Dr. David McLean & Dr. Jason Rivers
University of British Columbia Division of Dermatology
855 West Tenth Avenue
Vancouver, BC, Canada V5Z 1L7

Disposition and Demographic Data

Thirty patients were enrolled and one was lost to follow up without any evaluation. Baseline demographics showed 100% Caucasian patients, 22 males and 8 females

and mean age of 61 (SD 13). Eleven patients were judged to have had mild disease, 17 moderate and 2 severe.

Efficacy Data

1. Proportion of patients who achieved "cured" in global assessment:

	End of Treatment	30 days post-treatment
Visual assessment	14/29=48%	22/29=81%
Photographic assessment	13/29=45%	22/29=81%

Between visit 1 (day 60) and visit 2 (day 120), 7 patients discontinued treatment due to complete resolution; between visit 2 and visit 3 (day 180), 5 more discontinued due to "cure". Medication was no longer administered after day 180 despite protocol.

2. Lesion counts were only done for the last 10 enrolled patients and were not analyzed by dichotomization. The mean baseline count was 3.1; at end of treatment the mean count was 2.7; and at follow-up it was 0.9.

3. Patient and physician assessment of efficacy at the post-treatment follow-up visit was as follows:

	Patient evaluation	Investigator evaluation
Excellent	13 (45%)	13 (45%)
Good	3 (10%)	4 (14%)
Fair	3 (10%)	3 (10%)
Poor	10 (34%)	9 (31%)

Safety Data

1. Adverse Events. The report included adverse events and "concurrent illnesses" together. The total number of patients with adverse events was not given, but dermal adverse events alone occurred in 21/30 patients (70%). The AE list is as follows:

Body System	Adverse Event/Concurrent Illness
Body as a whole 9 (30%)	-allergic reaction 1, flu 1, headache 2, hernia 1, infection 3, back pain 2
Cardiovascular system 4 (13%)	-atrial arrhythmia 1, hypertension 3
Digestive system 1 (3%)	-tooth disorder 1
Endocrine system 1 (3%)	-diabetes mellitus 1
Metabolic and nutritional 1 (3%)	-hemochromatosis 1
Musculoskeletal system 3 (10%)	-arthritis 1, joint disorder 1, myalgia 1
Nervous system 7 (23%)	-dizziness 1, hyperesthesia 3, paresthesia 4
Respiratory system 6 (20%)	-asthma 2, bronchiectasis 1, emphysema 1, pharyngitis 1, rhinitis 1
Skin and appendages 21 (70%)	-ASR* 2, carcinoma 1, contact dermatitis 1, eczema 7, pruritus 6, rash 10, seborrhea 1, dry skin 4, skin ulcer 1, urticaria 1
Special senses 3 (10%)	-glaucoma 3
Urogenital system 1 (3%)	-uterine atony 1

*ASR=application site reaction.

Discontinuations due to adverse events. There were 12 discontinuations due to adverse events: contact dermatitis 1, pruritus 1, eczema 6, rash 2, hyperesthesia 2.

2. Tolerability. Patient evaluation showed tolerability to be fair to excellent in 69% of subjects (11 excellent, 5 good, 4 fair) but 31% (9 subjects) responded as "poor".

2. Clinical Laboratory tests. No clinically or statistically significant abnormalities were found for any variable tested in hematology or serum chemistry.

3. Provocative Use Test (PUT). Ten subjects participated (5 healthy volunteers and 5 patients). One subject (a patient) had a mild erythema, moderate vesiculation at the PUT site lasting for <24 hours. No other dermal events were reported. Serum for anti-diclofenac antibodies were negative for all samples.

Conclusions

1. This study does not support efficacy of diclofenac 3% gel in the treatment of AK under proposed labeling conditions because of protocol design.
2. Use of diclofenac 3% gel 1 Gm bid to the application site (twice the proposed dose) for up to 180 days appears to be generally well tolerated, with mild to moderate application site reactions being the most prevalent AEs reported
3. No evidence of systemic allergic sensitization to diclofenac was detected.

Additional Study on Gel Vehicle. An Open Study to Assess the Efficacy and Safety of Topical HYAL CT1101 Vehicle in theTreatment of Actinic Keratoses [TDHA-AK-CDN-93-01 (Vehicle)] [Conducted 1/24/95 to 7/21/95]

At the conclusion of Study TDHA-AK-CDN-93-01, a study on vehicle gel was added, to be done by the same Investigators, Drs. McLean and Rivers. This consisted of the same protocol as TDHA-AK-CDN-93-01, with the following differences:

- Study medication was the gel vehicle without diclofenac (lot number ULE2)
- Dosing was specifically to a 2" by 2" area with 1 Gm of gel bid (no defined area size in original study)
- Dosing was for 90 days only (up to 180 days in original protocol)
- Evaluations were done at 30 day intervals: baseline, day 30, day 60 and day 90 (no post-treatment visit) (vistis at 60-day intervals in original study)

Ten Caucasian patients were enrolled, with 8 completing treatment visits and 2 dropouts [lack of efficacy 1, AE (pruritus) 1]. One of the 8 completed patients had used alternative treatment (liquid nitrogen). There were 4 males and 6 females, aged 50-78 (mean 65) and baseline disease severity was mild in 8 and moderate in 2.

At the end of treatment, 2 patients were considered "cured" by global (visual and photographic) (20%). Patient and physician assessment of efficacy and tolerability are shown as follows:

	Efficacy		Tolerability	
	Patient evaluation	Investigator evaluation	Patient evaluation	Investigator evaluation
Excellent	3 (30%)	3 (30%)	6 (60%)	6 (60%)
Good	1 (10%)	1 (10%)	2 (20%)	2 (20%)
Fair	0	2 (20%)	1 (10%)	1 (10%)
Poor	6 (60%)	4 (40%)	1 (10%)	1 (10%)

The adverse event profile is:

Body System	Adverse Event/Concurrent Illness
Body as a whole 4 (40%)	-accidental injury 1, cellulitis 1, edema of face 1, infection 1, pain 1
Cardiovascular system 3 (30%)	-capillary fragility increase 1, migraine 1 hypertension 1
Digestive system 1 (10%)	-duodenal ulcer 1
Endocrine system 1 (10%)	-hypothyroidism 1
Hemic and lymphatic 1 (10%)	-lymphadenopathy 1
Musculoskeletal system 3 (30%)	-arthralgia 2, myalgia 1
Nervous system 2 (10%)	-dizziness 1, dystonia 1, paresthesia 1
Respiratory system 1 (10%)	-bronchitis 1
Skin and appendages 9 (90%)	-ASR* 2, acne 2, psoriasis 1, pruritus 5, rash 2, dry skin 1, skin ulcer 1
Special senses 2 (20%)	-glaucoma 1, conjunctivitis 1
Urogenital system 2 (2%)	-menopause 2

*ASR=application site reaction.

There were no clinically significant laboratory abnormalities detected.

Comment on the Vehicle Study This is an open study done after the original diclofenac protocol. It would have been useful to do it in parallel with the original study using the active, and blinded with randomization. As it is, there is little that can be concluded upon regarding efficacy, as AK is known to have some spontaneous regression over time. The safety data suggest that the vehicle is generally well tolerated.

8.2.7 Trial #7. An Open Study to Assess the Efficacy and Safety of Topical 3% Diclofenac in —— Hyaluronic Acid Gel (HYAL ST5101) in theTreatment of Actinic Keratoses (ST5101-GRK-01) [Conducted 3/28/94 to 3/17/95]

Comment This is an early exploratory, single-center, uncontrolled study and cannot be considered as adequate and well-controlled to support the indication. Only a summary of the methodology and findings will be presented in this review.

Design and Methodology of Study This was an open label study with a protocol similar to that of TDHA-AK-CDN-93-01 but with two differences:
(1) This study had a shorter planned treatment period - up to 180 days (earlier if cleared) with 3% diclofenac (HYAL ST-5101, synonymous with CT1101; lot number ULD2, containing HA from ———————— instead of 210 days in the Canadian study. [Note: nc patient was dosed for >180 days in the Canadian study; thus these two studies had similar treatment periods.]
(2) Lesion counts were only done at baseline in this study.
(3) Global and photographic assessments were not done at the 30-day follow-up visit, the last evaluation being at the end-of-treatment visit.
(4) PUT was not part of the protocol in this study.

Comment The same comments on the protocol for TDHA-AK-CDN-93-01 pertain.

Results

The Investigator was:
Dr. John Stratigos
Department of Dermatology and Venerology
Medical School
University of Athens
Greece

Disposition and Demographic Data

Twenty patients were enrolled and one was lost to follow up without any evaluation. Baseline demographics showed 100% Caucasian patients, 11 males and 9 females and mean age of 63 (SD 7). Ten patients were judged to have had mild disease, 9 moderate and 1 severe.

Efficacy Variables

1. Proportion of patients who achieved "cured" in global assessment:

	End of Treatment
Visual assessment	14/19=74%
Photographic assessment	13/11=45%

Between baseline and visit 1 (day 60), 6 patients discontinued due to complete resolution of target lesion(s); between visit 1 and visit 2 (day 120), 6 more discontinued due to "cure"; between visit 2 and visit 3 (day 180), 2 patients had complete resolution.

Comment Only end-of-treatment data are available. The 30-day post-treatment visit did not collect data on global or photographic assessment.

2. Patient and physician assessment of efficacy and tolerability at the post-treatment follow-up visit was as follows:

	Efficacy		Tolerability	
	Patient evaluation	Investigator evaluation	Patient evaluation	Investigator evaluation
Excellent	14 (74%)	14 (74%)	18 (95%)	18 (95%)
Good	3 (16%)	3 (16%)	1 (5%)	1 (5%)
Fair	2 (11%)	2 (11%)	0	0
Poor	0	0	0	0

Safety Data

1. Adverse Events. The report included adverse events and "concurrent illnesses" together. The total number of patients with adverse events was 11, and dermal adverse events alone occurred in 2 patients (#1: rash, dry skin and facial edema of moderate severity and #17: mild skin ulcer). The AE list is as follows:

Body System	Adverse Event/Concurrent Illness
Body as a whole 2 (7%)	-back pain 1, *face edema** 1
Cardiovascular system 2 (7%)	-coronary artery disorder 2
Endocrine system 2 (7%)	-hypothyroidism 1, hyperthyroidism 1
Hemic and lymphatic 1 (3%)	-anemia 1
Metabolic and nutritional 1 (3%)	-hyperlipemia 1
Nervous system 2 (7%)	-psychosis 1, vertigo 1
Skin and appendages 3 (10%)	-*dry skin* 1, *rash* 1, *skin ulcer* 1
Special senses 1 (3%)	-cataract 1
Urogenital system 2 (7%)	-prostatic disorder 1

*"adverse events" in italics; all others were classified as "concurrent illness"

Discontinuations due to adverse events. There were no discontinuations due to adverse events.

Comment The low incidence of dermal AE in this Greek study is unexplained.

2. Clinical Laboratory tests (CBC/Chemistry). No significant abnormalities were noted.

Conclusions

1. This study does not support efficacy of diclofenac 3% gel in the treatment of actinic keratosis under proposed labeling conditions because of protocol design.
2. Use of diclofenac 3% gel 1 Gm bid to the application site (twice the proposed dose) for up to 180 days appears to be generally well tolerated.

9 Overview of Efficacy

The controlled studies in support of the AK indication have been done in the U.S., Canada and Australia. There are 3 phase 3 trials, 2 in the U.S. and one in Canada. The following Table shows the studies for AK:

Study No.	Site(s)	Sample Size (M:F)	Dose	Treatment Duration	Sites	Arms	Dates
CONTROLLED							
CT1101-01	Australia	150 (89:61)	3%, 0.25 Gm/25 cm^2 bid	12 wk	3	2	10/13/94-6/25/95
CT1101-02	Australia	130 (73:57)	3% , ? Gm bid	8-24 wk	1	2	9/27/94-7/8/96
CT1101-03	U.S.	118 (89:29)	3%, 0.5 Gm/25 cm^2 bid	90 d	4	2	7/11/95-1/30/96
CT1101-04	Canada	195 (142:53)	3%, 0.5 Gm/25 cm^2 bid	30 or 60 d	6	4	8/3/95-2/6/96
CT1101-07	U.S.	111 (85:26)	3%, 0.5 Gm/25 cm^2 bid	90 d	1	2	3/4/96-11/21/96
UNCONTROLLED							
TDHA-AK-CDN-93-001	Canada	29 (22:8)	3%, 1 Gm bid	210 d	1	1	2/21/94-1/16/95
TDHA-AK-CDN-93-001add	Canada	10 (4:6)	vehicle, 1 Gm bid	≤90 d	1	1	1/24/95-7/21/95
ST5101-GRK-01	Greece	19 (11:8)	3%, 1 Gm bid	210 d	1	1	3/28/94-3/27/95

The 3 studies considered adequate and well controlled by the Applicant are shaded.

The uncontrolled studies were exploratory and will not be further elaborated upon. The Applicant has supplied adequate plus supportive controlled studies for NDA filing. It is noted that CT1101-03 and -04 were planned at the same time, purposely having different treatment periods (90 days for -03; and 30 and 60 days for -04). Study CT1101-07 was added subsequently so that there were two well-controlled studies with 90-day treatment period.

9.1 Dose Selection

No formal studies on dose ranging in AK have been performed. In the early stage of the development program, uncontrolled studies used 1 Gm of diclofenac gel bid without specification of the size of the area for application. For the two Australian phase 2 controlled studies with bid dosing, one did not specify the amount to be used per application, and the other used 0.25 Gm to an area of 5 cm x 5 cm. The three phase 3 trials were done with 0.5 Gm per 5 cm x 5 cm treatment "block" bid (up to 3 "blocks" per patient). There were no studies comparing the frequency or quantity in dosing.

There are problems with accuracy in dosing:

- One phase 2 study, CT1101-02, and the phase 3 studies CT1101-03 -04 and -07 allowed patients to use a vaginal applicator to deliver the required quantity of drug, or apply a "Finger Tip Unit" as the patient saw fit.
- In CT1101-01, where the dose was supposed to be 0.25 Gm/25 cm^2, the instruction was to apply the gel with an amount of the ——— This is the same description for 0.5 Gm ——— in the proposed labeling under DOSAGE AND ADMINISTRATION.

- The dose 0.5 Gm over an area of 25 cm^2 in the phase 3 trials is equivalent to 20 mg/cm^2, a quantity in great excess of what can normally be accommodated (10 times a thin film, 2 mg/cm^2). The excess gel would easily be subject to loss over clothing, pillows and bed sheets.

It may be concluded that the quantity of drug applied and bioavailable to the lesions in these studies can only be estimated but not defined.

The studies CT1101-03 and -04 together constitute one duration-ranging program (30, 60 and 90 days dosing).

9.2 Design and Endpoints in Controlled Studies

All controlled studies used Hyal's 3% diclofenac gel formulation intended for marketing. There was a change in the process of manufacturing the ingredient hyaluronate sodium. The phase 2 studies done in Australia used hyaluronan ——— while the phase 3 studies used product containing hyaluronan from ——— In addition, the doses in phase 2 studies were less than that in phase 3 or not defined (see discussion in Section 9.1 and Table under Section 9). However, since treatment might be stopped on complete clearance of lesions in all the studies (in addition to other reasons), the actual degree of drug exposure in these trials could vary. Moreover, a review of the data listings suggests that the "blocks" might not necessarily fit 5 cm x 5 cm areas (e.g., one side of nose, eyebrow, lip, canthum, or ear). This introduced further variability into dosing. Data on drug exposure will be discussed in Section 10.1.

All 5 studies were randomized, double-blind, vehicle-controlled, parallel-group studies comparing 3% diclofenac gel bid with vehicle gel bid. Enrollment criteria were similar. Apart from the phase 2 study CT1101-02, the controlled trials designated drug application to 5 cm x 5 cm treatment areas or "blocks". For the phase 3 studies, up to 3 "blocks" per patient were allowed. These "blocks" included the following regions: scalp, forehead, central face, arm and back of hand (excluding arms in CT1101-04). Patients were seen at visits 30 days apart during treatment, and in a follow-up visit 30 days post-treatment. The main differences in design and endpoints are shown in the following Table:

Study No.	Sites	Design Tr Duration	5 cm x 5 cm Tr "Blocks"	Dose per Application	Efficacy Endpoints					
					CLNS	TLNS	TTS	PGII	IGII	Histology
CT1101-01	3	84 d	x	0.25 Gm/"block"	*				*	
CT1101-02	1	≤24 wk		?					*	
CT1101-03	4	90 d	x	0.5 Gm/"block"	x	x		x	x	
CT1101-04	6	30 or 60 d	x	0.5 Gm/"block"	x	x	x	x	x	x
CT1101-07	1	90 d	x	0.5 Gm/"block"	x	x		x	x	

CLNS=cumulative lesion number score, TLNS=target lesion number score, TTS=total thickness score, PGII=patient's global improvement index, IGII=Investigator's global improvement index: for details on definition and scoring, see text on individual studies (identical definitions and scoring among the three phase 3 trials). Asterisk indicates endpoint similar to CLNS or IGII but with different names and scoring scales in CT1101-01 and -02. The 3 studies considered adequate and well controlled by the Applicant are shaded.

The Applicant designated multiple parameters as primary endpoints, and did not specify the time point for primary analysis. In the pre-NDA meeting, the Agency had stated to the Applicant that the primary endpoint would be the proportion of patients showing complete clearing of lesions at the follow-up visit 30 days after cessation of treatment.

Because the study design in CT1101-02 used a longer treatment period (up to 24 weeks), involvement of only one center, unspecified dosing, mandatory use of medicated sunscreen, lack of post-treatment evaluation, and difference in endpoints, this study is not considered adequate to support the application. However, the longer exposure provided supportive safety data. Similarly, although the Applicant considers CT1101-07 adequate and well controlled, there was only one study site.

9.3 Patient Numbers and Demographics in Controlled Studies

	Patient Numbers	
Study	Diclofenac	Vehicle
CT1101-03	58	59
CT1101-04	97 (d-30*, 49; d-60, 48)	98 (v-30, 49; v-60, 49)
CT1101-07	56	55
AK-CT1101-01	74	77
ST-5101-AUS-01 (CT1101-02)	65	65
Total	350	354

*d-30, d-60, v-30, v-60=diclofenac for 30 days, diclofenac for 60 days, vehicle for 30 days, vehicle for 60 days respectively. The 3 studies considered adequate and well controlled by the Applicant are shaded.

		Demographics	
		Diclofenac	Vehicle
Mean Age (Range)			
CT1101-03		65 (35-87)	65 (45-85)
CT1101-04	30-d*	67 (38-85)	67 (34-90)
	60-d	70 (47-86)	65 (45-83)
CT1101-07		64 (40-80)	68 (48-84)
CT1101-01		68 (27-87)	69 (36-89)
CT1101-02		70 (48-77)	72 (48-87)
Race			
CT1101-03	Caucasian	59	58
	Hispanic	0	1
CT1101-04		?	?
CT1101-07	Caucasian	56	55
CT1101-01		?	?
CT1101-02		?	?
Sex (M:F)			
CT1101-03		44:15	45:14
CT1101-04	30-d	33:16	35:14
	60-d	33:15	41: 8
CT1101-07		38:18	47: 8
CT1101-01		49:24	40:37
CT1101-02		39:26	34:31
Number of Treatment "Blocks" (1:2:3)			
CT1101-03		28:23: 7	32:21: 6
CT1101-04	30-d	25:18: 6	24:16: 9
	60-d	20:14:14	23:13:13
CT1101-07		54: 2: 0	55: 0: 0
CT1101-01		Only one "Block" treated in this study	
CT1101-02		Treatment on lesions, not on "Blocks"	

Baseline Lesion Severity		Mild	Moderate	Severe	Mild	Moderate	Severe
CT1101-03		21	33	5	18	33	8
CT1101-04	30-d	24	23	2	28	19	2
	60-d	29	19	0	28	19	2
CT1101-07		31	20	5	37	18	0
CT1101-01		27	36	10	16	45	16
CT1101-02							

*d-30, d-60, v-30, v-60=diclofenac for 30 days, diclofenac for 60 days, vehicle for 30 days, vehicle for 60 days respectively. Racial breakdown for Canadian (CT1101-04) and Australian studies (CT1101-01 and -02) not given; baseline severity for CT1101-02 not evaluated. The 3 studies considered adequate and well controlled by the Applicant are shaded.

9.4 Data in Support of Effectiveness

Phase 3 Studies

Results on the primary variable, proportion of patients with complete clearing of lesion counts (CLNS=0), for the two adequate and well controlled studies being considered, CT1101-03 and -04 are shown as follows:

Proportion Of Patients Experiencing Complete Resolution Of Lesions (CLNS*=0) At 30-d Follow-Up

	Diclofenac	Vehicle	p value
CT1101-03 90 days	27/58 (47%)	11/59 (19%)	<0.001
CT1101-04 30 days	7/49 (14%)	2/49 (4%)	0.2212
60 days	15/48 (31%)	5/49 (10%)	0.0214

*CLNS=cumulative lesion number score

The data of CT1101-03 demonstrate that Hyal's diclofenac is superior to vehicle in the treatment of AK with a 90-day regimen. CT1101-04 confirms this because of superiority demonstrated even with a 60-day regimen. Because of the significance shown at 60 days, it may be inferred that treatment for 90 days, if performed also in CT1101-04, would have also given very robust outcome as in CT1101-03. A 60-day regimen is currently supported by only one study. Acceptance of a 60-day course would have to depend on confirmation in an additional study. Although the Applicant did not consistently carry last observations forward for the ITT analysis or perform adjustments for multiplicity, the conclusion on effectiveness would not be affected because of the highly robust data obtained.

Findings from the secondary parameters confirm the primary analysis.

Meta-analysis by combining data across studies is not appropriate because of the different regimens in these studies, and will not be discussed.

In the third phase 3 trial, CT1101-07, comparison between diclofenac and vehicle for CLNS=0 at 30 days post-treatment did not reach statistical significance (diclofenac 18/53=34%, vehicle 10/53=18%; p=0.061). However, the differences in secondary variables including change in lesion counts and Investigator global highly favored diclofenac:

	Diclofenac	Vehicle	p value
ΔCLNS	-6.6	-4.5	0.006
IGII	2.7	1.9	0.009

CLNS=cumulative lesion number score, IGII=investigator's global improvement index

As shown in the Table in Section 9.3 on demographic data, CT1101-07 had more patients with baseline severity graded as moderate or severe in the diclofenac group (moderate 20, severe 5) than in the vehicle group (moderate 18, severe 0). This may be one of the factors accounting for the primary variable data not achieving significance. Another possibility is that the Investigator in this study tended to withdraw patients more readily when dermal AEs occurred, resulting in higher discontinuation rate and shorter exposure in the diclofenac group (65 days; 75 days for vehicle).

Although lesion mapping in the phase 3 studies would have provided an opportunity to determine true recurrence of regressed lesions vs occurrence of new lesions, the phenomenon of recurrence after treatment with Hyal's gel has not been explored. Additionally, it might have required longer follow up than was originally planned in the studies. It is noted that new lesions did manifest in the treatment "blocks" during the course of the study, but some of them also regressed post-treatment.

Phase 2 Studies

CT1101-02 will not be considered here, as it is not considered adequate and well controlled. As discussed above, CT1101-01 was a multi-center, randomized, double-blind, parallel-group, vehicle-controlled trial with a dosing period similar to that of CT1101-03 and -07 (84 days in -01 and 90 days in -03 and -07). This study lends data highly supportive of those obtained in phase 3. The primary variable, proportion of patients with complete lesion clearance at post-termination follow-up, was: diclofenac 17/45 (38%), vehicle 4/42 (10%); p=0.002. The secondary variables, lesion counts and percent change in lesion counts, were also very significantly different between treatment groups in favor of diclofenac (p=0.0009 and 0.0001 respectively).

AK lesion recurrence after treatment has not been explored. As the design of the phase 2 studies did not include exact mapping of the lesions, it would not have been possible to address this phenomenon.

9.5 Analysis of Efficacy Data by Covariates

Tables for the analysis of the proportion of patients with complete resolution of lesions (CLNS=0) at post-treatment follow-up visit in relation to various covariates are missing (Table 11.1-11.9 of Statistical Documentation in Integrated Summary of Safety and Efficacy, vol 1.46). These Tables for interaction analysis should be supplied.

9.5.1 Demographic Subsets

Race was not analyzed because of the very small number of non-Caucasians in the U.S. trials, and the unreported racial breakdown (probably mainly Caucasian) in the non-U.S. studies. Upon request, gender and age analyses were provided as follows, with combined data across the phase 3 trials for the primary variable:

		Proportion of Patients Experiencing CLNS=0 at 30 Days post-Treatment		
Subset		Diclofenac	Vehicle	p-value
Sex	M	51/145 (35%)	24/168 (14%)	<0.0001
	F	16/63 (25%)	4/44 (9%)	0.0634
Age	≤65	30/86 (35%)	12/90 (13%)	0.0019
	>65	37/122 (30%)	16/122 (13%)	0.0036

There were disproportionately fewer females than males in the AK studies. Moreover, a higher proportion of the female patients had lesions in the hands and arms than the males (50% in either treatment group for females; 21% in diclofenac and 24% in vehicle group for males). These may account for the difference in statistical significance in the proportion of patients developing complete resolution. Otherwise, age and gender do not appear to be important factors in the response to diclofenac treatment.

9.5.2 Anatomic Location of Treatment "Block"

In a submission dated 2/17/99, the following was provided for the phase 3 studies:

Anatomical Areas: Forehead, Central Face, Scalp And Neck

	Proportion of patients with CLNS=0 at 30 days Post-Treatment Follow-Up (LOCF)		
Study	Diclofenac	Vehicle	p-value
CT1101-03	22/42 (52%)	11/43 (26%)	0.0127
CT1101-04	22/84 (26%)	6/85 (7%)	0.0017
CT1101-07	17/35 (49%)	7/38 (18%)	0.0078
All Studies Combined	61/161 (38%)	24/166 (14%)	<0.0001

Anatomical Areas: Back Of Hand, Arm/Forearm

	Proportion of patients with CLNS=0 at 30 days Post-Treatment Follow-Up (LOCF)		
Study	Diclofenac	Vehicle	p-value
CT1101-03	10/25 (40%)	4/22 (18%)	0.1099
CT1101-04	2/18 (11%)	2/20 (10%)	0.9113
CT1101-07	2/21 (10%)	3/17 (18%)	0.4675
All Studies Combined	14/64 (22%)	9/59 (15%)	0.3689

Despite the fact that these studies were not powered to demonstrate efficacy in different anatomical regions, even the data from individual studies indicate that Hyal's diclofenac gel was very effective for lesions in the head and neck region, but those on the upper extremities were more resistant. However, the data on hand, arm and forearm lesions must be interpreted with caution, because of smaller sample sizes. It would be useful to have specific breakdown of the upper extremities data to distinguish between the effects on the arms and hands. Such information in labeling will be helpful to the prescriber.

The data for CT1101-04 had been pooled from treatment arms with shorter, and probably less than optimal durations of therapy. However, the dosing regimens in CT1101-03 and CT1101-07 were the same (0.5 Gm bid for 90 days). The difference between the treatment effects on upper extremity AK lesions in these two studies is not clear. One possibility, discussed under Section 9.4, may be that patients with AEs in CT1101-07 tended to be withdrawn early, and thus might have been deprived of a more adequate course of therapy.

9.5.3 Adverse Event Discontinuation

Because of the suggestion that resolution of AK lesions might be related to dermal reactions, the following analysis was made by the Applicant, using combined data from the three phase 3 studies:

	Terminated for AE	Not Terminated due to AE
Proportion of pts with CLNS=0 30 d Post-Treatment		
Diclofenac	7/22 (32%)	60/186 (32%)
Mean percent change in lesion count (CLNS)		
Diclofenac	-55% (N=22)	-64% (N=186)
Vehicle	-18% (N=9)	-41% (N=203)

These data show that the rate of clearing in diclofenac-treated patients was the same whether the patients were termination for AEs or not. There was slightly less reduction in lesion counts in diclofenac-treated patients who discontinued vs those not discontinued, while vehicle-treated patients who discontinued had much lower reduction. Because of the small number of patients terminated for AEs, statistical analysis has not been performed and is not expected to be reliable.

9.5.4 Other Covariates

Because of better power for analysis, the Applicant used the changes in lesion scores (TLNS) to examine interactions with the following covariates for diclofenac-treated patients in the phase 3 trials combined:

TLNS change from baseline (diclofenac group)

Total Dose per "Block"	<38 Gm	38-72 Gm	>72 Gm	
	-1.8	-2.6	-1.2	p=0.419
Baseline Severity	Mild	Moderate	Severe	
	-1.4	-1.8	-3.0	p=0.010
Fitzpatrick Skin Type	I	II	III	
	-1.3	-1.7	-1.6	p=0.664
Application Site Reaction	Presence		Absence	
	-1.4		-1.6	p=0.096

Apart from baseline disease severity, the above analyses do not reveal important influences on the changes in target lesion counts by the covariates examined.

9.6 Conclusions on Efficacy

1. Hyal's diclofenac gel is effective in the treatment of actinic keratosis with a bid dosing regimen for 90 days.
2. AK lesions of the scalp, forehead and face are more responsive to Hyal's diclofenac, while those in the extremities are less susceptible.
3. The long-term benefit has not been established, as the issue of lesion recurrence after cessation of therapy has not been addressed.

10 Overview of Safety

10.1 Safety Database, Exposure and Duration of Therapy

The Applicant submitted safety data on both AK and non-AK indications in the original NDA, and, in its 120-day Safety Update, provided more data from a completed ——— study, AT2101-015. The safety database to support the indication,

treatment of AK, consists primarily of patients from the following studies:

	Patient Numbers	
Study	Diclofenac	Vehicle
Controlled		
CT1101-03	58	59
CT1101-04	97 (d-30*, 49; d-60, 48)	98 (v-30, 49; v-60, 49)
CT1101-07	56	55
AK-CT1101-01	74	77
ST-5101-AUS-01 (CT1101-02)	65	65
Subtotal	350	354
Uncontrolled		
TDHA-AK-CDN-93-01	30	0
ST5101-GRK-01	20	0
Subtotal	50	0
Total	400	354

*d-30, d-60, v-30, v-60=diclofenac for 30 days, diclofenac for 60 days, vehicle for 30 days, vehicle for 60 days respectively

In addition, there are dermal safety studies and special provocation use tests. For data on non-AK indications, see Section 10.4.3.3.

Exposure to Study Medication in AK studies is shown as follows:

		Mean Total Use (Grams)		Mean Duration of Treatment (Days)	
		Diclofenac	Vehicle	Diclofenac	Vehicle
Controlled Studies					
CT1101-03		107 (78)*	127 (99)	75	80
CT1101-04	30 days	53 (46)	53 (40)	30	30
	60 days	112 (81)	101 (79)	62	58
CT1101-07		87 (84)	117 (117)	65	85
AK-CT1101-01		49 (49)	54 (54)	74	80
ST-5101-AUS-01		44**	79**	146	168
Uncontrolled Studies					
TDHA-AK-CDN-93-01		83**	–	84	–
ST5101-GRK-01		55**	–	141	–

*Figures for mean total dose given as: per patient (per 5 cm x 5 cm treatment "block").
**no treatment "blocks" specified in these studies.

Comments

1. The duration of treatment for Study CT 1101-04 were 30 or 60 days, but all other studies planned exposures for 84 days or more (12 weeks for CT1101-01, 90 days for CT1101-3 and -07, 168 days for CT1101-02, and 210 days for TDHA-AK-CDN-93-01 and ST5101-GRK-01). Thus, for the studies on AK alone, there were 303 patients treated with diclofenac gel for 12 weeks or more. The patient numbers exposed to Hyal's diclofenac gel during its development may be considered consistent with ICH Guideline E1A.
2. The actual exposure durations might be lower in some patients because of dropout due to treatment success, treatment failure and adverse events. However, the drug product has also been studied in other indications. Study 003-HA- —. a U.S. open trial with 70 patients, used diclofenac 3% gel at 0.5 Gm bid for 12 wk on ——— ——— Four other studies on — involved more than 70 patients using the drug product at the same dose for 8 weeks. In ——— studies, over 600 patients used 2 Gm of the gel four times daily (8 times the dose in the phase 3 AK trials) for 30 days. Although these studies spanned over a shorter duration, the total exposure per patient was more than 2.5 times the expected use for the AK indication.
3. Although the database provides support for the safety on the use of Hyal's diclofenac 3% gel, and the formulation in these studies has been consistent, there has been a change in the process of manufacturing the hyaluronic acid ——— in CT1101-03, -04 -07 and -09, ——— in all others). This issue will be addressed in Section 10.6.
4. It is unclear whether the exposure in terms of mean total dose is of any relevance.

The dose to be administered to each 25 cm^2 treatment "block" was to be 0.25 to 0.5 Gm per application (10 to 20 mg/cm^2). This was in great excess of a thin film of gel on the skin (10 to 20 times greater) and would easily be liable to loss through contact especially with clothing, pillows and bed sheets for the evening doses. Therefore, the degree of actual exposure to medication is uncertain.

10.2 Significant/Potentially Significant Events

Deaths One death occurred in CT1101-07 (#019 cardiomyopathy, congestive heart failure and arrhythmia).

"Serious Adverse Events" These are shown in the following Table:

Study Pt no. & treatment	Adverse Event (severity/relationship to treatment)	Comments
Controlled Studies		
CT1101-03		
01-008 diclo*	BCC (mild/unlikely)	Recurrence on nose
04-001 diclo	Pelvic injury (sev/unlikely)	
01-030 vehicle	BCC (mild/unlikely)	Recurrence of BCC not at target site
02-004 vehicle	Motor vehicle accident (sev/unlikely)	
CT1101-04		
5019 v-30	BCC (moderate/unlikely)	BCC lesion found prior to therapy
2010 v-30	Angina (moderate/unknown)	
6001 v-30	HIV positive (mild/unlikely)	
1020 v-60	SCC (mild/unlikely)	History of SCC
CT1101-07		
019 diclo	Death from CHF	See above under "Deaths"
003 diclo	Chest pain (sev/unrelated)	Diagnosed as heartburn
034 diclo	Prostate cancer (mild/unlikely)	
040 diclo	Kidney infection (sev/unlikely)	
052 diclo	SCC (mild/unlikely)	Diagnosed (forehead) at last treatment visit
031 vehicle	CHF (sev/unlikely related)	History of CHF
054 vehicle	SCC (mild/unrelated)	Not on treated area
AK-CT1101-01		
104 diclo	Melanoma (moderate/unlikely)	Not on treatment site
176 diclo	Sick sinus syndrome (sev/unlikely)	
029 vehicle	Spine adenocarcinoma (sev/unrelated)	
066 vehicle	Melanoma (mild/unlikely)	Existed prior to study start
132 vehicle	Elective surgery (severe/unlikely)	Surgery for "sun-damaged" hand
ST-5101-AUS-01		
019 diclo	Skin melanoma (sev/unlikely)	History of melanoma
079 diclo	Angina (mild/unlikely)	
100 diclo	BCC (moderate/unlikely)	History of BCC, excision of recurrence
125 diclo	Angina (mild/unlikely)	
Uncontrolled Studies		
TDHA-AK-CDN-93-01	No Serious Adverse Events reported	
ST5101-GRK-01	No Serious Adverse Events reported	
PK and Dermal Safety Studies		
EP105 4 diclo	Cellulitis of i.v. site (sev/unlikely)	
— 9502 276 diclo	Arrhythmia (sev/unlikely)	
— 0046 210 diclo	Cholecystectomy (sev/unlikely)	

*d-30, d-60, v-30, v-60=diclofenac for 30 days, diclofenac for 60 days, vehicle for 30 days, vehicle for 60 days respectively, diclo=diclofenac, BCC=basal cell carcinoma, SCC=squamous cell carcinoma, CHF=congestive heart failure, sev=severe.

Discontinuations due to Adverse Events

The Applicant admits that there are discrepancies in the reporting of discontinuations, as some Investigators had neglected to fill in the Termination/End-of-Study Form to indicate withdrawal from study, since patients were required to return for the 30-day

post-treatment follow-up. Stated simply, there has been a confusion between discontinuation from treatment and discontinuation from the study. This has led to a difference between individual clinical study reports and the safety database. The following Table is derived from data in the reviews of studies in Section 8 (see above):

		Diclofenac	Vehicle
Controlled Studies			
CT1101-03		ASR 6, ASR* 7	ASR 2, ASR* 2
CT1101-04	30-d	ASR 2	ASR 1
	60-d	Contact dermatitis 3, ASR 1	ASR 1
CT1101-07		Contact dermatitis 18, pruritus 1, ca prostate 1, cardiomyopathy 1	ASR 1, ASR* 1, contact dermatitis 1,heart failure 1
AK-CT1101-01		ASR 9, ASR* 6, sick sinus syndrome 1	Adenocarcinoma 1, ASR 1, bursitis/edema 1
ST-5101-AUS-01		ASR* 14, rash (due to Renitec®)	ASR* 2
Uncontrolled Studies			
TDHA-AK-CDN-93-01		Contact dermatitis 1, eczema 6, ASR* 5	Not applicable
ST5101-GRK-01		None	Not applicable

*ASR (application site reaction) here includes rash, pruritus, dry skin, edema, paresthesia, hyperesthesia at treatment site: those given with asterisk in the Table may not necessarily be classified as such in the report, and ASR without asterisk refers to actual designation as such in the report.

Comment Most of the discontinuations were due to application site reactions, which occurred more frequently in the active treatment groups.

Duration of Exposure in Patients Discontinued Due to AEs in Phase 3 Studies

	Mean Duration of Treatment					
	Diclofenac			Vehicle		
	N	Days	% of Duration for Entire Group*	N	Days	% of Duration for Entire Group
Controlled Studies						
CT1101-03	13	60.0	80	4	13.8	17
CT1101-04 30 days	2	21.0	70	1	5.0	17
60 days	4	49.5	80	1	24.0	41
CT1101-07	20	36.9	57	4	17.8	21

*Duration for the discontinued patients/duration for entire treatment group expressed as percentage.

Comment Patients who discontinued in the active treatment groups had mean exposures lasting 57%-80% of those for the entire groups using diclofenac. In CT1101-07, these dropouts were withdrawn earlier (mean 36.9 days; 57% of the 65 days for all diclofenac patients), but those in other phase 3 trials used diclofenac for 70% to 80% of the period completed by diclofenac subjects. Thus, most patients who discontinued due to AE tolerated diclofenac treatment for substantial lengths of time and were not withdrawn early. Patients who used vehicle and discontinued due to AEs tended to withdrew much earlier and had exposure to the vehicle for 17%-41% of the periods completed by other vehicle patients.

10.3 Overdose Exposure

The drug product has low systemic absorption, making overdose through the topical

route unlikely. For overdose due to ingestion, general measures to treat poisoning with NSAIDs should be used, and supportive and symptomatic treatment be given for complications including renal failure, GI irritation, convulsions and respiratory depression.

Comment The above systemic manifestations are based on acute toxicity studies with diclofenac across a number of species (see Pharm/Tox review), but not specifically with Hyal's gel. The effect of hyaluronan in acute toxicity has not been defined, but appears to be unlikely. Hyaluronan concentration in Hyal's gel is —— and ingestion of 1 liter of gel would expose a person to —— of the polysaccharide (less than ——— .

10.4 Other Safety Findings

10.4.1 ADR Incidence Tables

See Appendices for adverse event Tables. The cumulative data from AK trials are shown in Appendix VI.

The major AEs that might be considered related to treatment involved application site reactions (ASRs). These included primarily dry skin, pain, paresthesia, pruritus, rash, contact dermatitis and exfoliation (see Appendix VI). Adverse events were not actively solicited so that the subjective events such as pruritus and paresthesia might have been underestimated. The Applicant has reclassified some of the application site events (such as paresthesia, tingling, etc.) and moved them from under the "Nervous System" to under "application site reaction", which belongs to "Skin and Appendages". Grouping under ASR has the advantage of not splitting up AEs to reduce incidence but might mask the real incidence of individual events. An analysis of ASR ensues:

Number Of Patients Experiencing ASR by Dose Per Treatment "Block" and by Duration (Phase 3 Studies)

	Number of Patients with Specific ASRs (% of Sub-Group)*					
	Diclofenac Daily Dose (Gm)/"Block"			Vehicle Daily Dose (Gm)/"Block"		
ASR	<0.8	0.8-1.2	>1.2	<0.8	0.8-1.2	>1.2
dry skin	13 (24)	13 (23)	16 (23)	9 (18)	11 (19)	10 (13)
pain	12 (22)	15 (27)	19 (27)	15 (30)	16 (28)	17 (21)
paresthesia	5 (9)	13 (23)	13 (19)	6 (12)	11 (19)	8 (10)
pruritus	19 (35)	30 (54)	27 (39)	38 (76)	25 (44)	32 (40)
rash	20 (37)	23 (41)	28 (40)	14 (28)	10 (18)	11 (14)
cont. dermatitis	11 (20)	17 (30)	13 (19)	3 (6)	0	3 (4)
exfoliation	10 (19)	10 (18)	8 (11)	4 (8)	3 (5)	9 (11)
	Number of Patients with Specific ASRs (% of Sub-Group)*					
	Diclofenac Total Dose (Gm)/"Block"			Vehicle Total Dose (Gm)/"Block"		
ASR	<32	32-72	>72	<32	32-72	>72
dry skin	11 (20)	17 (27)	14 (23)	10 (18)	4 (9)	16 (19)
pain	16 (29)	14 (22)	16 (26)	18 (33)	7 (15)	23 (27)
paresthesia	8 (15)	11 (17)	12 (19)	10 (18)	1 (2)	14 (16)
pruritus	24 (44)	22 (35)	30 (48)	34 (62)	26 (57)	35 (41)
rash	23 (42)	23 (37)	25 (40)	11 (20)	14 (30)	10 (12)
cont. dermatitis	14 (25)	14 (22)	13 (21)	2 (4)	1 (2)	3 (3)
exfoliation	12 (22)	6 (10)	10 (16)	3 (5)	3 (7)	10 (12)

ASRs bolded indicate those having significant difference between treatment groups in overall incidence. *N for diclofenac 180, vehicle 187.

	Number of Patients with Specific ASRs (% of Sub-Group)**					
	Diclofenac Treatment Duration (Days)			Vehicle Treatment Duration (Days)		
ASR	<30	30-60	>60	<30	30-60	>60
dry skin	2 (8)	21 (24)	26 (27)	1 (5)	8 (11)	21 (18)
pain	8 (32)	23 (26)	21 (22)	5 (24)	13 (18)	32 (28)
paresthesia	2 (8)	14 (16)	19 (20)	5 (24)	5 (7)	22 (19)
pruritus	11 (44)	35 (40)	47 (48)	12 (57)	39 (53)	54 (47)
rash	10 (40)	35 (40)	38 (39)	4 (19)	12 (16)	23 (20)
cont. dermatitis	8 (32)	22 (25)	17 (18)	1 (5)	1 (1)	4 (3)
exfoliation	2 (8)	13 (15)	18 (19)	0	2 (3)	15 (13)

ASRs bolded indicate those having significant difference between treatment groups in overall incidence. **N for diclofenac 210, vehicle 210.

Number of Patients Experiencing ASR by Oral NSAID Use (Phase 3 Studies)

	Number of Patients with Specific ASRs (% of Sub-Group)*			
	Diclofenac		Vehicle	
ASR	NSAID+**	NSAID-	NSAID+	NSAID-
dry skin	19 (27)	30 (21)	10 (15)	20 (14)
pain	22 (31)	30 (21)	19 (28)	33 (23)
paresthesia	12 (17)	23 (16)	14 (21)	18 (12)
pruritus	38 (54)	55 (39)	32 (48)	73 (50)
rash	34 (48)	49 (35)	13 (19)	26 (18)
cont. dermatitis	22 (31)	25 (18)	3 (4)	3 (2)
exfoliation	18 (25)	15 (11)	10 (15)	7 (5)

ASRs bolded indicate those having significant difference between treatment groups in overall incidence. *N for diclofenac 211, vehicle 212; **NSAID+=with oral NSAID use, NSAID-=no oral NSAID use.

Number Of Patients Experiencing ASR by Age and by Sex (Phase 3 Studies)

	Number of Patients with Specific ASRs (% of Sub-Group)*							
	Diclofenac		Vehicle		Diclofenac		Vehicle	
ASR	≤65 yrs	>65 yrs	≤65 yrs	>65 yrs	M	F	M	F
dry skin	20 (23)	29 (23)	14 (16)	16 (13)	30 (20)	19 (30)	20 (12)	10 (23)
pain	31 (36)	21 (17)	20 (22)	32 (26)	40 (27)	12 (19)	40 (24)	12 (27)
paresthesia	15 (17)	20 (16)	17 (19)	15 (12)	25 (17)	10 (16)	24 (14)	8 (18)
pruritus	44 (51)	49 (40)	44 (49)	61 (50)	61 (41)	32 (50)	70 (47)	26 (59)
rash	39 (45)	44 (35)	16 (18)	23 (19)	62 (42)	21 (33)	28 (17)	11 (25)
cont. dermatitis	22 (25)	25 (20)	1 (1)	5 (4)	37 (25)	10 (16)	3 (2)	3 (7)
exfoliation	12 (14)	21 (17)	6 (7)	11 (9)	25 (17)	8 (13)	11 (7)	6 (14)

ASRs bolded indicate those having significant difference between treatment groups in overall incidence. *N for diclofenac 211, vehicle 212; M=male, F=female.

Comment There does not appear to be significant interactions between ASR incidence and the covariates: dose (daily and total), duration of treatment, use of oral NSAIDs, age and sex.

Resolution of Local Adverse Events Present at End of Treatment

The Applicant has provided an analysis of adverse events occurring at the end of treatment in the phase 3 trials. As most of the non-application site adverse events were unlikely to be related to treatment, only the data on "application site reactions" occurring at the end of treatment are summarized here:

		Severity			Days to Resolution		Outcome at 30-day Follow-Up Visit			
AE	N	mild	mod	sev	mean	Npat	CR	w\seq	NR	unk
Diclofenac Group	211									
Alopecia	2	2	0	0	7	1	1		1	
Contact dermatitis	39	14	20	5	17	36	32	1	5	1
Dry skin	24	19	5	0	13	23	20	1	3	
Edema	3	1	2	0	6	3	3			
Exfoliation	10	8	2	0	17	10	9		1	
Hyperesthesia	1	0	1	0	40	1			1	
Maculopapular rash	2	0	2	0	22	2	1		1	
Pain	20	11	8	1	10	20	19		1	
Paresthesia	11	8	2	1	12	11	9		2	
Photosensitivity	1	1	0	0	69	1			1	
Pruritus	35	21	11	3	12	35	31	1	3	
Rash	44	28	13	3	14	43	39	1	4	
Skin carcinoma	1	1	0	0	7	1			1	
Skin hypertrophy	2	2	0	0	16	2	2			
Vesiculobullous rash	2	1	1	0	35	1	1		1	
Vehicle Group	212									
Alopecia	1	1	0	0	26	1	1			
Contact dermatitis	2	2	2	0	22	2	2			
Dry skin	10	9	1	0	9	9	9			1
Edema	0									
Exfoliation	8	8	0	0	14	8	8			
Hyperesthesia	0									
Maculopapular rash	0									
Pain	8	3	4	1	7	6	7			1
Paresthesia	5	3	2	0	8	5	5			
Photosensitivity	1	1	0	0	1	1	1			
Pruritus	16	12	4	0	11	15	13	1	1	1
Rash	8	6	2	0	9	8	7		1	
Skin carcinoma	0									
Skin hypertrophy	0									
Vesiculobullous rash	0									

AE=adverse event, N=number of patients with adverse event at the end of treatment, mod=moderate, sev=severe, Npat=number of patients with data to calculate time to resolution, CR=complete resolution, w\seq=with sequelae, NR=not resolved at the time of analysis, unk=unknown.

Comment The great majority of local adverse events at the end of treatment had resolved by 30 days post-treatment. Only 25/197 (13%) of those events in the diclofenac group and 2/59 (3%) in the vehicle group did not completely resolve by follow-up. There was only one instance of each type of AE being unresolved in each treatment group at the 30-day follow-up, with the exception of the following: contact dermatitis 5, dry skin 3, paresthesia 2, pruritus 3 and rash 4.

10.4.2 Laboratory Findings, Vital Signs, ECGs

There were no consistent significant laboratory findings. Vital signs are not pertinent. ECGs were not included in the clinical studies.

10.4.3 Special Studies

10.4.3.1 Pharmacokinetics Studies

These have been reviewed by the Biopharm Reviewer. Three pharmacokinetic (PK) studies were presented. In addition, serum diclofenac blood levels were measured from samples taken in the phase 3 trials at the end of treatment. These samples were originally intended for detection of antibodies to diclofenac.

10.4.3.1.1 Open PK Studies

The 3 PK studies were all multiple-dose, open, 2-way cross-over, randomized studies; 2

of the studies used the current formulation of 3% diclofenac gel (but with hyaluronic acid [redacted]. These studies are summarized in the following Table:

Study No.	Sample Size (M:F)	Age	Treatment and dose	Treatment Duration	Subjects	Tmax (hrs)	Cmax (ng/mL)	AUC (ng.hr/mL)	t1/2 (hr)
BIBRA 91/148/PL U.K	6 (2:4)	18-55	• — Hyal's diclof gel 2Gm tid •1% diclofenac (emulgel) • • (7d WO between)	7d 7d	healthy volunteers	•	•	•	•
BP329 LAB Canada	23 males	18-45	•3% Hyal's diclof gel 2 Gm tid Voltarol 75 mg qd (9d WO between)	6d 6d	healthy volunteers	•	4.49 4.7	9.09 31.6	4.5 15.9
EP105 Canada	12 (4:8)	19-40	•3% Hyal's diclof gel 2 Gm qid - a) intact skin b) compromised skin (14d WO between)	7d 7d	dermatitis patients	12.6 12.7	59.6 76.1	468.2 632.1	• 11.2

•could not be determined; diclof=diclofenac, WO=washout; dermatitis patients= patients with atopic dermatitis.
Voltarol data shaded for Study BP 329 LAB, and compromized skin data shaded for Study EP105.

Comments

1. BIBRA 91/148/PL did not study the formulation to be marketed. BP329 LAB showed that systemic absorption with Hyal's 3% diclofenac gel was very low, especially when compared with Geigy's oral Voltarol (75 mg diclofenac). Study EP105 showed that compromised skin had greater absorption of diclofenac than intact skin in patients with atopic eczema, but the difference was not statistically significant. When compared with oral diclofenac in healthy volunteers, the dose-corrected extent of absorption with Hyal's diclofenac gel was 12% for compromised skin and 9% for intact skin. There was also no correlation between lesion size and extent of absorption in atopic eczema patients.
2. The expected use in AK per treatment "block" (0.5 Gm/25 cm^2 bid) is one-eighth of the amount in Study EP105 (2 Gm/100 cm^2 qid). This allows for an even greater safety margin.
3. In study EP105, application of study medication was primarily to extremities. Absorption from the skin in the head and neck region has not been adequately determined other than through therapeutic drug monitoring (see below, Section 10.4.3.1.2). This information is important, as the efficacy of Hyal's diclofenac gel is primarily towards lesions in the scalp, forehead and face rather than those in the extremities.

10.4.3.1.2 Therapeutic Drug Monitoring in Phase 3 Trials

Samples from patients in the phase 3 studies (CT1101-03, -04 and -07) were taken within 24 hrs of the last dose before cessation of treatment. In these studies, patients applied 0.5 Gm of test medication to each 5 cm x 5 cm treatment "block". There were 86 samples and 76 were from 60 patients who applied Hyal's diclofenac gel to a single treatment "block"; 10 were from patients who had multiple treatment "blocks" (contrast oral diclofenac data above).

The results from the 60 patients treated for one "block" (0.5 Gm/25 cm^2 bid) showed that when treated for up to 105 days, they had low serum levels of diclofenac (mean 11.5 ng/mL over 24 hrs post-dose and ***17 ng/mL*** over 6 hrs post-dose). Four patients were treated for 3 "blocks" (1.5 Gm/75 cm^2 bid; maximum allowed in the trials): their mean serum diclofenac level in the first 6 hrs post-dose was ***20 ng/mL***.

Comments
1. The PK study EP105 was done with drug mostly applied to the upper extremities. Data on absorption through head and neck skin have come primarily from therapeutic drug monitoring. However, an analysis of these data from the clinical trials with respect to the location of the "treatment blocks" has not been presented.
2. These findings suggest that there is little relationship between systemic absorption and the topical dose applied.
3. The mean level for patients treated for 3 "blocks" (*20 ng/mL*) is comparable to those from EP105 with atopic eczema patients (2 Gm/100 cm^2 qid; *15 ng/mL* for intact skin and *24 ng/mL* for compromised skin 6 hr post-dose). Subjects in EP105 used Hyal's gel containing haluronan by ——— rather than from ——— used in phase 3 trials and for that intended for marketing). These data suggest possible greater systemic bioavailability with the diclofenac gel containing HA from ——— (comparable mean blood levels with lower dosing). There may be important but unexplored differences in secondary structure or viscosity affecting release of the active drug.

Serum diclofenac levels were also measured in 51 samples from patients who completed one of the phase 3 studies, CT1101-07, and were in the active treatment arm. These samples were randomly taken from day 0 to day 48 post-treatment. Apart from one sample taken on day 7 (—ng/mL), levels were below quantifiable limit beyond day 2.

Comment Topical treatment of AK with Hyal's 3% diclofenac gel results in low systemic absorption and does not appear to show accumulation with post-treatment release.

10.4.3.2 Dermal Safety Studies

The following studies have been performed:

Study Number	Study	Dosing	Subjects of Study	Source of HA in Test Drug
— 9500	irritancy test	single application	healthy volunteers	
— 9502	sensitization test	9-application induction in 3 wk; single application for challenge	healthy volunteers	
— 9503	phototoxicity test	single application	healthy volunteers	
— 9504	photoallergenicity test	6-application induction in 3 wk; single application for challenge	healthy volunteers	
— 0046	sensitization test	9-application induction in 3 wk; single application for challenge	patients on stable oral NSAIDs	
— 97-1619-70 (CT1101-09)	sensitization test	9-application induction in 3 wk; single application for challenge	healthy volunteers	
AT-2101-14 (CT1101-08)	sensitization & irritancy test	single 48-hr application	patients previously exposed to 3% diclofenac gel	
No number		0.5 Gm bid 7-day application	AK — pts with previous dermal reaction	

10.4.3.2.1 ——— 9500. Primary Skin Irritation Potential of 3% Sodium Diclofenac Gel

This study consists of a single application of the following to the backs of healthy volunteers: (1) 3% diclofenac Gel (lot no ULD2), (2) gel vehicle (lot no. UEE1) and (3) 1% sodium lauryl sulfate (SLS) solution. The test materials (0.2 ml) were applied to the paraspinal region and each test site was immediately covered by gauze pad held in place with surgical tape for 24 hrs. The sites were evaluated 0.5 and 24 hrs after removal. Grading was for erythema and edema on a 5-point scale (0=none, 1=very

slight, 2=mild, 3=moderate and 4=severe). The study was performed at ———

Results. Nineteen patients were enrolled (Caucasians:Blacks=14:5, M:F=2:17, age 18-61). There were no positive edema scores. Erythema scores were:

Score	0	1
3% diclofenac gel	17/19	2/19
Vehicle gel	18/19	1/19
1% SLS	8/19	11/19

Adverse Events reported in the trial were: backache 1, pruritus 2.

Comment This study used a single application and did not address cumulative irritancy. It is not of regulatory value.

10.4.3.2.2 ——— 9502. Evaluation of Contact Sensitization Potential of 3% Sodium Diclofenac Gel

This study evaluates both contact sensitization and cumulative irritancy potential in healthy volunteers. It consists of nine 24-hr induction applications over 3 weeks and a 2-week rest period, followed by a single 24-hr challenge application at the original and a naïve site with the test materials: (1) 3% diclofenac Gel (lot no. ULD2), (2) gel vehicle (lot no. UEE1) and (3) 0.1% sodium lauryl sulfate (SLS) solution. The test materials (0.2 ml) were applied to the paraspinal region and each test site was immediately covered by gauze pad held in place with surgical tape for 24 hrs. During induction, the patch sites were evaluated 24 or 48 hrs after removal for irritancy (scale of 0-4 based on erythema). Challenge sites were examined at 24 and 48 hrs after removal. Clinical laboratory tests (CBC and serum chemistry) were done only at the beginning of the study. The study was performed at ———

Results. There were 116 patients enrolled (Caucasian:Black:Hispanic:Asian =91:23:1:1; M:F=20:96; mean age 34 for males and 38 for females), with 102 completing the study. The mean cumulative irritation scores were 0.07843±0.34 (diclofenac), 0.07843±0.34 (vehicle) and 0.06863±0.25 (SLS). At the challenge phase, grade 1 rating (mild erythema) was observed only at 24 hrs for vehicle (1 case) and 0.1% SLS (2 cases), but not diclofenac.

Adverse events reported at the test sites were pruritus and burning:

	Diclofenac site	Vehicle site	SLS site
Pruritus	8	10	8
Burning	3	2	2

All reactions considered as mild except one at vehicle site (pruritus, moderate)

Other AEs reported were: nausea 1, cold symptoms 7, headache 6, pruritus (tape) 5, sinusitis 3, backache 2, stomach pain 1, menstrual cramps 1, muscle spasms 1, migraine 1, renal stone 1, toothache 1, constipation 1, sinus headache 1, ankle pain 1, laceration 1, poison ivy 1, bruised foot 1, nervousness 1 and dysrhythmia 1. There were

2 discontinuations due to adverse events: GI upset 1 and dysrhythmia 1. No comments can be made on the clinical lab tests, as they were only done at baseline.

Comments
1. No evidence of sensitization by diclofenac gel was observed. This suggests that its sensitization rate is no greater than 3% as the study had only 102 subjects. The Applicant has since done another study (CT1101-09) with greater enrollment to allow for a better risk evaluation.
2. Unlike the 21-day irritancy testing, this study uses discontinuous patch application (9 24-hr applications over 3 weeks). The diclofenac drug product is no more irritating than the vehicle; both showed cumulative irritancy similar to that of 0.1% SLS.

10.4.3.2.3 ——— 9503. Phototoxicity Potential of Sodium Diclofenac Gel

The study of phototoxic potential involved single application of 0.2 ml of sodium diclofenac gel (lot no. ULD2) and 0.2 ml of vehicle (lot no. UEE1) on separate areas (2 cm^2) of the backs of healthy volunteers for 24 hrs followed by long wave UV (UVA) irradiation (16-20 J/cm^2). A duplicate set of patches did not receive irradiation. The patch sites were examined for edema and erythema at 1, 24, 48 and 72 hrs after patch removal with a 5-point scoring scale (0=none, 1=very slight, 2=mild, 3=moderate and 4=severe). Clinical laboratory tests were only done at baseline. The study was performed at ———————————

Results. There were 25 subjects (all Caucasians, aged 18-65, M:F=9:16), and all completed the study. No edema was observed. One subject showed very slight erythema at visit 2 (visit for patch removal, timing not specified: whether before or after irradiation) which resolved by 24 hrs. Adverse events reported were: headache 3, tooth extraction 1, and cough 1.

Comment This study has an adequate sample size. It used UVA alone instead of both UVA and UVB for irradiation. A UVB component should have been added, as the absorption spectrum of diclofenac includes UVB (peaks at ——— nm).

10.4.3.2.4 ——— 9504. Evaluation of Contact Photoallergy Potential of Sodium Diclofenac Gel

Photoallergenicity was evaluated with a protocol involving induction with 6 applications to the same site in the back over 3 weeks (2 applications per week) followed by a 2-week rest period and a single reapplication for challenge in healthy volunteers. Each application was covered with a sheet of gauze pad held in place with surgical tape for 24 hrs. During induction, UVB exposures at 2 MED were given to areas of 1 cm^2 within the patch sites immediately after patch removal, the MED having been determined for each subject prior to induction. At challenge, test patches were made in duplicate and upon removal, one set of sites received UVA at 16-20 J/cm^2. The test materials were 0.2 ml of diclofenac (lot no. ULD2) and vehicle (lot no. UEE1) gels as well as distilled water. Evaluation for sensitization was at 1, 24, 48 and 72 hrs after removal of the challenge patch, and used the scale in the following Table. Clinical laboratory tests were only done at baseline. The study was conducted by ———————————

Scoring of Skin Reactions

0	no reaction
1	reaction readily visible but mild, unless appended with letter grade (see E or F below) [Mild reactions include weak but definite erythema, & weak superficial skin responses such as glazing, cracking or peeling.
2	definite papular response (append E or F or S if appropriate.]
3	definite edema (append E or F or S if appropriate)
4	definite edema and papules (append E or F or S if appropriate)
5	vesicular/bullous eruption

E – presence of strong erythema at patch site, F – presence of strong effects on superficial layers of skin, including fissures, a film of dried serous exudate, small petechial erosions and/or scabs, S – presence of a reaction spreading beyond test site, X – patch omitted due to previous strong reaction(s).

Results. Among 31 subjects screened (all Caucasians, M:F=6:25, aged 27-64), 28 subjects were enrolled and 27 completed the trial. During the induction phase, erythema was observed (score=1 only) with the following frequency among the 27 subjects: diclofenac 2, vehicle 5 and distilled water 7. No erythema was noted for any site at any time in the challenge phase. No edema was observed in induction or challenge phases. The following adverse events were reported: scratched retina 1, arthritis 1, headache 1, URI 1, asthma/allergies 1 and skin infection of left cheek 1.

Comment The irradiation should have included both UVA and UVB.

10.4.3.2.5 —— 0046. Evaluation of Contact Sensitization Potential of Sodium Diclofenac Gel in Subjects who Require Oral, Chronic NSAID Therapy

It has been reported that a patient presenting with a widespread, itchy, erythematous, maculopapular eruption following oral ingestion of diclofenac gave a positive patch test with 0.075 mg/mL (0.0075%) of diclofenac solution, presumably in water; the test was positive after 48 and 72 hrs (Romano, 1994). Because of this concern, the Applicant performed this study to evaluate development of contact sensitivity to diclofenac in such patients. This study was similar to —— 9502, with the following differences:

- Subjects were chronic NSAID users for painful conditions who were otherwise healthy.
- The 9 induction patches were put on the deltoid region of the upper arm, with diclofenac (lot no. VGD6) on one side, and vehicle (lot no. WCE7) on the other. SLS was not used.
- Patches stayed for 48 or 72 hrs before removal, depending on the day of application during the week (24 hrs in —— 9502), and removal was by —— personnel.

The study was performed by —— all of ——

Results. Enrollment consisted of 108 subjects (aged 21-85, with mean of 56; M:F=24:84; Caucasians:Blacks:Hispanics:others=100:5:1:2; diclofenac user: other NSAID user=19:89) and 105 completed the study. The diclofenac gel patches produced mild erythema in 2, and papules in 1 of the subjects after 5 applications during induction. No positive reactions with diclofenac or vehicle gels were observed at challenge.

Adverse events were reported in the following systems:
body as a whole (pain 4, headache 10), digestive system (cholecystectomy 1, diarrhea 2, dyspepsia 7, gastritis 1),

musculoskeletal system (arthralgia 2, myalgia 8), nervous system (paresthesia 1), respiratory system (bronchitis 1, cold symptoms 2, hiccups 1, pharyngitis 1, pneumonia 1, rhinitis 2, sinusitis 1), skin and appendages (laceration 1, pruritus 10, purpuric rash 1, rash 3, toenail removal 1, red ant bite 1, pain 1), special senses (conjunctivitis 1) and urogenital system (cystitis 1, urinary tract infection 3)

Among these, 8 cases of pruritus, 1 case of myalgia, 1 case of pain (tenderness at patch site) and 1 case of paresthesia were considered to be possibly or probably related to the treatment.

Comments
1. As administration via the oral route might in fact be conducive to tolerance, this study with chronic NSAID users was not useful in elucidation of the real sensitization potential of topical diclofenac. A proper study using an adequate number of healthy volunteers would be needed to determine sensitization potential.
2. If the concern was to determine type IV sensitivity to diclofenac developed previously, a simple 48-hr patch test would have been adequate.
3. This study with continuous application of test material for 3 weeks established that the diclofenac 3% gel tested was of low irritancy potential.

10.4.3.2.6 CT1101-09 (——— 97-1619-70). Evaluation of Contact Sensitization Potential of 3% Sodium Diclofenac Gel in Normal Healthy Subjects

This study used the same methodology as ——— 0046 but on healthy subjects. It also had a larger sample size (232; 108 in ——— 0046). The test materials were diclofenac gel 3% (lot no. DT81) and vehicle gel (lot no. DT83), to be covered with occluded ——— patches. The gels used in this study contained hyaluronan obtained by

Results. There were 232 subjects enrolled (aged 18-86; M:F=40:192; Caucasians:Blacks:other=229:2:1), and 205 completed the study. Findings on irritation during induction showed:

	Diclofenac	Vehicle
transient mild (grade 1) erythema	85	57
transient moderate (grade 2) erythema	3	3
papules	2	0

In the challenge phase, the only positive reaction at 48 hrs after patch removal was mild erythema (grade 1) observed in one diclofenac site. The same subject (#1124) had transient moderate erythema and edema at the diclofenac site 30 minutes after patch removal. Upon rechallenge, there was also transient moderate erythema with papules.

Adverse events were reported in the following systems:
Body as a whole (light headedness 1, headache 50, body aches 1, fever 2, chills 2), digestive system (heartburn 4, diarrhea 6, dyspepsia/stomach ache 4, nausea 10, stomach cramps 10, abdominal pain 3, indigestion 1), musculoskeletal system (jaw pain 1, ankle pain 1, back pain 1, muscle aches/soreness 3), nervous system (nervousness 1), respiratory system (cough 2, cold symptoms 4, head congestion 8, runny nose 1, sore throat 5 sinus infection 3, URI 3, wheezing 1, flu 1, sinus congestion 5, sinus pain 3, sinus pressure 2), skin and appendages (itching on sites 4, burning on sites 1, burning sensation in right arm and hand 1, burn on left hand 1) and special senses (otitis media 3, oral surgery 1, root canal 1, menstrual cramps 1)

The AEs of skin and appendages were considered to be probably or definitely related to treatment, except for the burn on the left hand. Those possibly related to treatment

were: wheezing 1, muscle aches/soreness 1, lightheadedness 1, and all the cases of headache and digestive system AEs.

Comments
1. This study used an appropriate sample size and healthy volunteers.
2. The results suggest that diclofenac gel 3% is of low sensitization potential. The transient moderate erythema occurring 30 minutes after patch removal (#1124) has been attributed by the Applicant to irritation, and this subject also showed mild to moderate erythema during induction phase (application 1 moderate, applications 2, 3, 4 and 6 mild). However, the mild erythema observed at 48 hrs after patch removal in this same subject has not been explained. Sensitization has not been ruled out, especially since a similar reaction occurred with rechallenge.
3. Despite a greater number of positive reactions with diclofenac gel 3% vs vehicle gel, cumulative irritancy scores of the drug product and its vehicle did not show statistically significant difference.

10.4.3.2.7 CT1101-08 (AT2101-14) A 48-Hour Diagnostic Patch Test with Hyal's 3% Diclofenac Topical Gel and Diclofenac in Inert Bases in Patients Previously Exposed to Hyal's 3% Diclofenac Topical Gel (Study dates: 8/12/96-10/18/96)

The Health Protection Branch, Health and Welfare of Canada had been concerned about the safety of topical NSAIDs with respect to sensitization potential. This study was conducted to address this concern, and involved a single 48-hr open label application in patients previously exposed to 3% diclofenac gel for ——— or AK for at least 2 weeks. It consisted essentially of diagnostic patch testing. Test materials (15-20 µL) were applied at individual skin sites in — chambers occlusively attached to the arm or back with ——— tape patch. The patch was removed 48 hrs later and the site evaluated 1 hr after patch removal and 48 hrs later. Patients with "highly probable", "probable" or "possible" allergic contact dermatitis (see below for definitions) were to undergo PUT with repeat application over 14 days. Test substances included:

- Hyal's diclofenac 3% gel (lot no. KZ50225, batch no. XAD10; containing hyaluronan by ———
- diclofenac ——→ and 3% in petrolatum
- diclofenac ——— and 3% in ethanol.

Each dermal reaction was classified according to

-	negative	
?+	doubtful	faint erythema
+	weak (nonvesicular)	erythema, infiltration, possibly papules
++	strong (vesicular)	erythema, infiltration, papules, vesicles
+++	extreme	bullous reaction
IR	irritant reactions	
NT	not tested	

Criteria for sensitization:

- Erythema (mild, moderate, severe)
- Infiltration/edema (mild, moderate, severe)
- Fine structure (discrete papules, papulovesicles, coalescing vesicles)
- Surface distribution
- Area involved

Investigators evaluated each reaction as irritant or allergic based on their clinical judgment and Hyal's training as follows:

Allergic	Irritant
Persistent across day 3* to day 5 &/or	Transient temporally &/or
More marked between days 3-5	Maximum by day 3
Only appearing at day 5	
Tending to spread	Erythema often sharply delineated/discrete but patchy
Usually palpable, eczematous, possibly vesicular	Follicular or poral, pustular, possibly bullous
Local edema	No local edema

*day 3 being day of patch removal and day 5 48 hrs after patch removal.

After the study, *the Day 5 data* were reviewed by Hyal and allergic contact dermatitis was determined with the following criteria:

- Highly probable — all diclofenac sites rated "allergic" but none at control sites
- Probable — all 3 high-dose diclofenac sites "allergic" but none at controls
- Possible — any diclofenac site "allergic", but none at controls
- Unlikely — any other combination of responses

Comments

The criteria for determining allergy to diclofenac are arbitrary but acceptable. They address contact allergy (type IV) reaction to diclofenac. They do not detect other hypersensitivities (e.g., type I); nor do they address sensitivity to other components in Hyal's formulation.

Results

Enrollment included patients who previously participated in the following studies:

studies: AT2101-12, TDHA-PC-CDN-92-001-AR, AT2101-02, AT2101- — 93-01

AK studies: CT1101-03, CT1101-04

Investigators and numbers of patients enrolled are shown as follows:

Investigator	Location	N	Investigator	Location	N
CA Birbara, M.D	Worcester, MA	13	Dr. S. Roth	Phoenix, AZ	53
J Caldwell, M.D	Dayton Beach, FL	8	Dr. A. Russell	Brampton, Ont., Canada	20
S Cohen, M.D	Trumbell, CT	7	Dr. J. Wolfe, Jr.	Houston, TX	15
S Daniels, M.D	Houston, TX	3	Dr. JR Taylor	Miami, FL	15
RM Fleischmann, M.D	Dallas, TX	5	Dr. S. Kang	Ann Arbor, MI	16
J Kaine, M.D	Sarasota, FL	3	Dr. E. Tschen	Albuquerque, NM	14
D Kirby, M.D	Melbourne, FL	4	Dr. J. Rivers	Vancouver, BC, Canada	16
H Offenberg, M.D	Gainesville, FL	8	Dr. K. Barber	Calgary, Alta., Canada	4
SR Richard, M.D	Richmond, VA	6	Dr. N. Shear	Toronto, Ont., Canada	8
J Rutstein, M.D	San Antonio, TX	7	Dr. W. Carey	Montreal, PQ, Canada	30
			Dr. L. Guenther	London, Ont., Canada	20
			Dr. Y. Poulin	Ste-Foy, PQ, Canada	18

Data on demographics were not presented. All patients had past exposure to Hyal's 3% diclofenac gel for at least 2 weeks at therapeutic dosage for their indication being studied — AK). The duration between last exposure and the study was 1 to 32 months.

Of 266 patients who participated, 53 (20%) had one or more positive reactions (irritant or allergic) at day 3 or day 5, with 19 (7%) having reaction(s) at day 5. Incidence of reactions at 48 hrs for the test materials can be illustrated here:

	Hyal's Diclof 3%	Diclof/Petrolatum — 3%		Diclof/Ethanol — 3%		Petrolatum	Ethanol
All Patients N=266							
Irritant	1 (0.4%)	3 (1.1%)	1 (0.4%)	4 (1.5%)	6 (2.3%)	2 (0.8%)	1 (0.4%)
Allergic	5 (1.9%)	2 (0.8%)	3 (1.1%)	4 (1.5%)	8 (3.0%)	0	1 (0.4%)
—Patients N=138 (AT2101-08)							
Irritant	1 (0.7%)	2 (1.4%)	1 (0.7%)	2 (1.4%)	3 (2.2%)	2 (1.4%)	1 (0.7%)
Allergic	0	0	0	0	0	0	0
AK Patients N=128 (CT1101-08)							
Irritant	0	1 (0.8%)	0	2 (1.6%)	3 (2.3%)	0	0
Allergic	5 (3.9%)	2 (1.6%)	3 (2.3%)	4 (3.1%)	8 (6.3%)	0	1 (0.8%)

*Diclof=diclofenac

According to the Applicant's criteria, 9 of the patients (3%), all from previous AK, but not — studies, had "allergic" contact dermatitis:

Allergy to to Diclofenac	Patient ID	Dermal Reaction in Previous Study	Previous Reaction Max intensity
Highly probable	#43-010	Exfoliation, erythema, stinging, rash, itch	mild
Probable	#49-003*	"Contact dermatitis"	severe
Possible	#41-002	Burning, itch, peeling, bleeding	severe
Possible	#42-007	Edema, erythema, peeling, crusting	mild
Possible	#48-004	Erythema	mild
Possible	#48-012	Pruritus, erythema, rash, edema	severe
Possible	#48-030	Dry skin	mild
Possible	#49-016**	Eczematous dermal reaction	mild
Unlikely	#44-009	None	

*patient had previous negative PUT; **patient had previous positive PUT.

Comment It is unclear why the "allergic reactions" only occurred in patients with AK. Patients with AK are more likely to have sun-damaged skin but increase in sensitivity to topical medications is uncertain. A large proportion of patients (26/48=59%) who had a reaction rated as irritant or allergic at any time (1 hr or 46 hr after patch removal) also showed some reaction to the ethanol and/or petrolatum patches. Since it is unlikely that ethanol would remain in the patch for any significant part of the 48 hrs of exposure, irritancy to material(s) in the patch — chamber) cannot be excluded.

The 8 patients considered having at least "possible" allergic contact dermatitis to diclofenac (se above Table) were given open provocative use test (PUT) at 0.5 Gm bid for 14 days, using a site of 5 cm x 5 cm over the inner upper arm (one side for active and one side for vehicle) as the target area [diclofenac gel lot no. not mentioned, batch number DT76A]. The sites were evaluated on days 8 and 15. No systemic reactions were reported. Six out of the 8 patients gave a positive application site reaction to Hyal's diclofenac gel, but not to vehicle gel:

Reaction at 48-hr Patch Test	Pt ID	Result of PUT
Highly probable	43-010	+++
Probable	49-003*	+
Possible	41-002	-
Possible	42-007	++ (early termination due to reaction)
Possible	48-004	++
Possible	48-012	++
Possible	48-030	-
Possible	49-016**	++ (early termination due to reaction)

*patient had previous negative PUT; **patient had previous positive PUT.

Before doing the PUT study, and based on one highly probable outcome (#43-010), the Applicant predicted that in the general population of —— AK patients, the maximum expected rate of allergic contact dermatitis to diclofenac would be 1.7%. If probable and possible cases are also considered, the rate could be up to 4.8%. After the PUT study, the Applicant concludes that with 6/266 positive for allergic reaction, the maximum predicted incidence of allergic contact dermatitis would be 4.4% with 95% confidence.

Comment This calculation was based on all the 266 patients enrolled in the 48-hr patch testing. However, as all the positive reactions were only among AK patients, the incidence would have to be recalculated based on the 128 AK patients tested. The study report did not supply information on previous dermal reactions in the clinical trials for the entire patient population. It did, however, tabulate the presence/absence of previous reactions in the clinical trials for the 53 subjects who had any positive reaction in the current study, CT1101-08. Among AK patients, ***24/28 (86%)*** had previous dermal reactions to the Hyal's diclofenac gel. Of the —patients, ***8/25 patients (32%)*** had previous reactions, despite using a larger dosage (2 Gm bid; 0.5 to 1.5 Gm bid for AK). Since application site reactions occurred in ***34%*** of patients given diclofenac in CT1101-03 and ***17 to 29%*** (29% in 30-day and 17% in 60-day groups) in CT1101-04 (the 2 AK trials from which patients of the current study [CT1101-08] were drawn), it appears that the AK patients coming from CT1101-08 were ***highly selected***. In the absence of further information on the entire sample of AK patients selected to undergo 48-hr patch testing with respect to their dermal reaction status in the original AK trials, the predictive value derived by the Applicant (maximum of 4.4% allergic contact dermatitis) is unfounded.

Adverse Events. There were no serious adverse events. There was one case of severe AE: headache, and all other AEs were mild or moderate. They are listed as follows:

System (Total Pt Numbers)	Adverse Events
Musculoskeletal (20)	puffy fingers 1, aches/pains 8, joint stiffness 2, joint pain 3
Respiratory or ENT (8)	cold 2, sore throat 2, cough 1, cold sore 1, rhinitis 1, watery swollen eyes 1
CNS (15)	headache 9, dizziness 1, lightheadedness 1. fever 1, fatigue 1, heavy sensation of head 1, hot sensation of head 1
Genitourinary (3)	bladder frequency/urgency 1, vaginitis 1, urinary tract infection 1
Endocrine (1)	hyperglycemia 1
Gastrointestinal (9)	nausea 4, queasiness 1, appetite loss 2, stomach acidity increase 2
Dermatological (20)	itching 15, rash 2, skin tingling 1, skin warm 1, urticaria 1
Patch site reactions (17)	itching 10, rash 2, tingling 1, burning 1, irritation 2, heat sensation 1

Comments and Conclusions on CT1101-08

1. This study was done to allay concerns of the Health Protection Branch, Health and Welfare, Canada.
2. It is unwarranted to draw conclusions on sensitization potential from a single 48-hr patch testing.
3. It does not address non-type I hypersensitivities.
4. It does not address sensitivities to non-diclofenac components in Hyal's gel.
5. It does provide some idea on previous sensitization (type IV) to diclofenac, which is a real phenomenon documented in the literature.
6. In this study, dermal reactions to Hyal's diclofenac gel were shown to be due to irritant or allergic effects in AK patients, but only to irritant effect in —— patients.
7. The PUT data showing lack of reaction to gel vehicle support the inference that the sensitivity was to diclofenac and not to other ingredients of the gel.
8. Insufficient information on previous dermal reactions in the entire study sample of CT1101-08 makes it difficult to estimate the true risk of allergic contact dermatitis in the general population of AK subjects treated with Hyal's diclofenac 3% gel.

10.4.3.2.8 Detection of Antibodies to Diclofenac in Sera from Patients Who Used Hyal's Diclofenac Gel in Clinical Trials

Detection of serum antibodies for diclofenac was performed in the laboratory of Dr. Steven Leeder, Hospital for Sick Children, Toronto, Canada. This used the methodologies of (a) ——————— The sera were obtained from patients in the clinical trials involving Hyal's diclofenac gel, some of whom were about to undergo PUT. The results are shown in the following Table:

	Number of Pts with Samples Tested	Reaction in Clinical Trial	Antibody Detection
AK Studies			
TDHA-AK-CDN-93-001	5* (plus 5 healthy controls)	eczematous	Neg#
CT1101-03	18*	only some had reaction	Neg#
CT1101-04	191*	only some had reaction	Neg# except 2##
CT1101-07	110*	only some had reaction	Neg# except 7##
— Studies			
TDHA-PC-CDN-92-001-AR	8*	localized dermal	Neg#
AT2101- —93-01	5**	information not given	Neg#
AT2101-06	2	rash/erythema/itch	Neg#
— Study			
003-HA- —	4	rash/skin irritation	Neg#

*6/18 were to undergo PUT in CT1101-03; number of patients undergoing PUT in CT1101-04 not given; and 20/110 were to undergo PUT in CT1101-07. All 10 subjects of TDHA-AK-CDN-93-001 and 8 patients of TDHA-PC-CDN-92-001-AR were to undergo PUT with samples pre- and post-PUT for testing.

**7 samples from 5 patients, with 4 samples known to be after challenge.

#for both pre- and post-PUT samples, if available.

##2 samples from 1 patient in CT1101-04; 7 samples from 5 patients in CT1101-07.

Nine samples were reported to be positive (2 from CT1101-04 and 7 from CT1101-07). However, review of the raw data from the 2 samples from patient 03-015 in CT1101-04 did not show evidence of positivity, and no positive results could be discerned from the data presented in the report. The 7 positive samples in CT1101-07 were from 5 patients as shown below:

Pt ID	Pre-PUT1	Pre-PUT3
1-005	+	-
1-018	+	no sample
1-038	+	+
1-052	+	+
1-070	+	-

Comments

1. None of these 5 patients in CT1101-07 underwent PUT. The pre-PUT1 samples were taken at baseline before start of treatment in the clinical trial. The Investigator showed that these positive reactions were directed towards the carrier protein, and in all instances, the reactivity was with the ——— but not —— Moreover, two of the patients with initial positive samples (pre-PUT1) gave subsequent negative samples after initiation of treatment (pre-PUT3). Thus, the positive reactions were probably not directed towards diclofenac.
2. Antibodies to dicofenac are not expected if the sensitivity is a type IV reaction. Absence of IgE antibodies suggests that a type I reaction in these patients who have used topical diclofenac would be unlikely, even if they might have had dermal reaction to Hyal's gel.

Conclusion on Studies to Dectect Antibodies to Diclofenac

No antibodies to diclofenac have been documented in patients using Hyal's diclofenac gel.

10.4.3.2.9 Provocative Use Tests (PUT)

The process involved a 7-day challenge with Hyal's diclofenac gel applied to the inner aspect of the upper arm with a dose previously used in the clinical trials. In addition to 16 patients in the — program, there were 34 patients and 5 healthy volunteers in the AK program who underwent PUT (total 55 subjects):

	Dose	Patients in Clinical Trial Active	Vehicle	Healthy Volunteers
AK Studies				
TDHA-AK-CDN-93-01	1 Gm bid	5		5
CT1101-03	0.5 Gm bid	6		
CT1101-04	0.5 Gm bid	13	3	
CT1101-07	0.5 Gm bid	6	1	
—Studies				
TDHA-PC-CDN-92-001-AR (AT2101-06)	2 Gm qid	10		
AT-2101- — 93-01 (AT2101-02)	2 Gm qid	6		
Total		46	4	5

In 48% of those previously treated with Hyal's diclofenac gel and undergoing PUT (22), a positive response developed. Neither the 5 healthy volunteers in TDHA-AK-CDN-93-001 nor the 4 patients treated with vehicle gel in the phase 3 AK studies experienced any reaction to the active gel during PUT. The data for the 46 patients who previously used active drug can be shown as follows:

Reaction	Erythema	Edema/Vesiculation	Prutitus	Burning
None	27	34	27	39
Mild	11	7	11	4
Moderate	8	5	7	0
Severe	0	0	1	3

Comment PUT elicited dermal reaction in fewer than half of the patients who previously used Hyal's diclofenac and showed reaction. The majority of the reactions in PUT were mild or moderate in severity. The redevelopment of a reaction does not distinguish irritant from allergic response and little inference can be drawn from the above data. It is of interest to note that the 4 patients showing reactivity to vehicle during the clinical trial did not respond in PUT; thus sensitivity to components in the vehicle has not been demonstrated.

10.4.3.3 Safety Data from Studies on non-AK Indications

The Applicant has a safety database with 1209 patients treated with their diclofenac gel, 911 with vehicle and 110 with Geigy's diclofenac cream (Voltaren).

Study	Site(s)	Pt Numbers (M:F)	Regimen	Duration	Control	Design
003-HA- —	U.S.	70 (24:46)	3%, 0.5 Gm bid	12 wk		open
TDHA- — AUS-92-001	Aus	49	3%, 0.5 Gm bid	8 wk	vehicle	parallel, db, rand
TDHA- — AUS-92-002	Aus	75	3%, 0.5 Gm bid	8 wk	vehicle	parallel, db, rand
TDHA — CDN-92-002	Can	16	3%, 0.5 Gm bid	8 wk	vehicle	parallel, db, rand
TDHA — CDN-92-003	Can	16	3%, 0.5 Gm bid	8 wk	vehicle	parallel, db, rand
At2101- — 93-01	U.S.	119 (33:36)	3%, 2 Gm qid	30 d	vehicle	parallel, db, rand
8.1 AT-2101-12	U.S.	391 (153:238)	3%, 2 Gm qid	30 d	vehicle	parallel, db, rand
8.1 AT-2101-15	U.S./Can	616 (198:218)	3%, 2 Gm qid	30 d	vehicle	parallel, db, rand
TDHA-PC-CDN-92-001-AR	Can	110 (40:70)	3%, 2 Gm qid	30 d	vehicle	parallel, db, rand
PN-AT-2101-03	U.K.	197 (81:116)	3%, 2 Gm qid	30 d	vehicle	parallel, db, rand
TDHA- — PA-CDN-92-001-RS	Can	69 (38:31)	3%, 2 Gm qid	7 d	vehicle	parallel, db, rand
TDHA- — PA-AUS-93-002-LR	Aus	90 (32:58)	3%, ? frequency	7 d	vehicle	parallel, db, rand
AT-2101-PC-AST-93-001	Ger	111 (23:83)	3%, 2 Gm qid	7 d	Emulgel (CIBA)	Xover, db, rand
AT-2102 (US)	U.S	147 (47:100)	3%, 2 Gm qid-bid	?	N/A	Dose optimization
TDHA- — PA-CDN-92-002-PN	Can	8 (3:5)	3%, 2 Gm qid	?	vehicle	parallel, db, rand

db=double-blind, rand=randomized, Xover=cross-over, AK=actinic keratosis, ——— Can=Canada, Aus=Australia, Ger=Germany

In — trials, there were 684 patients treated with diclofenac and 550 with vehicle gel. On average, they were treated for 16 days (2 Gm qid) on target ———. In studies on ———, the dose used was similar to that in AK studies but the incidence of dermal AE was again smaller. A comparison with the AK data is shown as follows:

		Total Dermal AE	Rash	Pruritus	Pain
AK	diclofenac	82%	39%	44%	25%
	vehicle	75%	38%	50%	25%
—	diclofenac	16%	7%	4%	3%
	vehicle	27%	11%	13%	5%
———	diclofenac	41%*	11%	23%	7%
	vehicle	32%	16%	19%	13%

*also including 14 patients (11%) with contact dermatitis not shown in the Table.

Comments

1. The reason for the higher incidence of dermal AE in AK patients is unclear, but may be related to the longer duration of treatment and the condition of the skin in AK. The safety data in non-AK indications lend only minor support to the proposed indication, because of the lower incidence of AE in these other indications and shorter exposure periods in most of these studies.
2. The integrated report on safety data in AK, ——— (vol 1.50) has Tables 14 and 18 missing.

The following "serious" adverse events were reported:

	Diclofenac	Vehicle
TDHA- — CDN — 03	Chest pain 1	Renal failure/death 1
CT1101-CDN-93-01	Heart attack 1	
TDHA-PA-CDN-92-001-RS		Pancreatitis 1
AT2101-15	CHF 1, renal stone 1	Cholecystitis 1
AT2101-012	Transient ischemic attack 1	Abdominal pain 1, pneumonia 2, vertigo 1, *H. pylori* infection 1
AT2101-02	Basal Cell carcinoma 1	

In addition, Hyal's diclofenac has been [redacted] treatment of [redacted], and one case of [redacted] reaction with swollen lips has been reported.

Comment Apart from the possibility of an allergic reaction in the patient using diclofenac for [redacted] the serious AEs reported in studies of non-AK indications do not appear to be treatment-related.

10.4.4 Drug-Demographic Interactions

No clinically meaningful differences between the sexes for incidence rates of the most commonly reported ASRs were found; nor was there a higher risk in the elderly (defined as 65 years or older) for experiencing dermal events (see Section 10.4.1 for analysis). There have been too few non-Caucasians studied to make comparisons for effects of race.

Comments
1. *Post-hoc* subset analyses were not powered to detect subtle differences.
2. The Applicant should demonstrate safety of their product in non-Caucasians.

10.4.5 Drug-Disease Interactions

The clinical trials were done with exclusion of patients having conditions which might confound the data on efficacy or safety. The Applicant performed analyses to assess the incidence of ASRs in the presence/absence of concomitant allergy, liver and GI abnormalities identified at baseline, treatment "blocks", Fitzpatrick score, and baseline severity of AK. The results showed either negative interaction or small effects which were difficult to interpret because of inadequate patient numbers.

10.4.6 Drug-Drug Interactions

The clinical studies prohibited use of confounding medications but not oral NSAIDs. In one exploratory open study, ST-5101-AUS-01, a sunscreen ([redacted] +15) was to be used daily immediately after morning dose of the blinded gel treatment. Neither oral NSAIDs nor sunscreens appear to have had an impact on the incidence or severity of adverse events in the trials.

10.4.7 Withdrawal Phenomena/Abuse Potential Not applicable

10.4.8 Human Reproductive Data

No human data are available. There is no evidence of teratogenicity by diclofenac in preclinical studies involving mice, rats and rabbits. The effects of diclofenac on labor and delivery in pregnant women are unknown; as with other NSAIDs, it is possible that it may inhibit uterine contractions and delay delivery. Because of the risk of premature closure of the ductus arteriosus, prostaglandin-inhibiting drugs should be avoided in late pregnancy.

10.5 Pediatric and Geriatric Use

AK is not an indication applicable to pediatric use. The AE profile in the elderly (>65 years of age) does not appear to be different from that in younger patients.

10.6 Special Considerations for Diclofenac

Diclofenac is an NSAID which has the following potential toxicities:

- GI upset including diarrhea, indigestion, nausea, constipation, flatulence, peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer
- Hemoglobin decrease, leukopenia, thrombocytopenia, eosinophilia, hemolytic anemia, aplastic anemia, agranulocytosis, purpura, allergic purpura
- Liver enzyme abnormalities
- Renal effects: As a class, NSAIDs have been associated with renal papillary necrosis and other abnormal renal pathology including dose-dependent decrease in prostaglandin synthesis and, secondarily, in a reduction of renal blood flow, which may precipitate overt renal failure. Diclofenac may increase plasma levels of lithium, digoxin and methotrexate and increase cyclosporine's nephrotoxicity. [Diclofenac metabolites are eliminated primarily by the kidneys; patients with significantly impaired renal function should be more closely monitored.]
- Cross-reactivity, including bronchospasm, between aspirin and other NSAID in aspirin-sensitive patients
- Increase in platelet aggregation time through inhibition of prostaglandin synthesis

However, since the absorption for Hyal's diclofenac gel is small, it is not anticipated that these toxicities would be likely. The potential for such effects should be properly conveyed in the label.

The possibility of sensitization has been extensively addressed by the Applicant. The drug product is probably of low contact sensitization potential, as only one in 205 healthy volunteers appeared to have developed allergic contact dermatitis after repetitive insult patch testing. However, the potential for sensitization in AK patients may be higher, as shown by the greater incidence of dermal AE in AK studies when compared to those for non-AK indications. At this point there are no data to confirm this assumption. There is no evidence of type I sensitivity to the drug product demonstrated in the development program of Hyal's diclofenac gel.

10.7 Special Considerations for Hyaluronate

Hyal's diclofenac gel contains — sodium hyaluronate (hyaluronan) as inactive ingredient. Although the formulation has not been changed in the development program for AK, there has been a change in the manufacturing process of the hyaluronan. Earlier studies used a product with hyaluronan —— The more recent ones, however, used preparations having hyaluronan —— The product proposed for marketing will contain —— hyaluronan.

Clinical studies that used —— hyaluronan include the 3 phase 3 trials (CT1101-03, -04 and -07), as well as the dermal safety study for sensitization potential (CT1101-09) and that for 48-hr patch testing (CT1101-08). There has also been one — study (AT2101-15) done using the product containing —— hyaluronan.

There are three safety issues regarding the source of hyaluronan:

Systemic bioavailability of diclofenac. This issue has been addressed in Section 10.4.3.1.2.

Effects of contaminants. The nature and quantity of —— present, if any, would determine the issues to be addressed. It appears unlikely that the hyaluronan would contain sufficient —— material to be of concern, since other marketed —— products such as —— have not posed such an issue. The specifications given by the Applicant on HA are acceptable to the Pharm/Tox

Reviewer. The ——————————————— and there is no ——————— involved in the production of HA.

Allergic response. The Applicant has addressed the issue of allergenicity extensively in the development program of this drug product (see Section 10.4.3.2). Specifically, sensitization potential was investigated in a study testing the active product containing ——————— hyaluronan and its vehicle (CT1101-09), with no evidence of sensitization to the vehicle documented. Moreover, patients in the phase 3 trials (which also used the product with ——————— hyaluronan) who had dermal reactions to vehicle were rechallenged with PUT with negative results (see Section 10.4.3.2.9).

Therefore, pending no unforeseen contaminants discovered in the CMC or Microbiology reviews, it is concluded that the safety issues on ——————— hyaluronan have been adequately addressed.

10.8 Safety Conclusions

1. Use of Hyal's diclofenac gel in AK is associated with the development of dermal reactions in a substantial proportion of patients. These reactions are mostly mild to moderate in intensity, and tend to recover completely by 30 days post-treatment.
2. Hyal's diclofenac gel is probably of low sensitization potential, as only one in 205 healthy subjects showed possible evidence of sensitization upon challenge in a sensitization study. However, its real incidence in AK cannot be extrapolated from healthy volunteers, since other data suggest greater potential for skin of AK patients to react unfavorably.
3. No evidence of type I hypersensitivity to diclofenac has been demonstrated in patients who used Hyal's diclofenac gel.
4. Systemic bioavailability of diclofenac is low from its intended use.
5. Hyal's diclofenac gel may be considered generally well tolerated for its intended use in the treatment of AK.

11 Resistance Not applicable

12 Risk-Benefit Analysis

Risks:

- Dermal reactions – high, usually of mild to moderate intensity and tend to recover by 30 days post-treatment
- Sensitization potential (types I or IV) – low in healthy subjects, probably low in AK patients
- Systemic toxicity – low, because of low systemic bioavailability
- Teratogenicity and other pregnancy effects – teratogenicity not known, other pregnancy effects low, because of low systemic bioavailability
- Off-label use for non-AK conditions – high
- long-term risks – not determined, especially the possibility of masking the development of skin cancer

Benefits:

- Effective in the treatment of AK, a precancerous condition

- Long-term benefit not established: issue of recurrence after cessation of therapy not addressed
- Efficacy in non-Caucasians not demonstrated

Analysis:
The high risks of mild to moderate dermal reactions and off-label use may be addressed with labeling. Other risks are low or theoretical. The benefit of resolution of a precancerous condition is high.

It may be concluded that the benefit outweighs the risks. The availability of other products for AK does not affect this analysis. Notwithstanding the availability of these products, Hyal's diclofenac gel may still have a role in the armamentarium of agents for the treatment of AK.

13 Conclusions
Hyal's 3% diclofenac gel may be considered safe and effective in the treatment of AK under properly labeled conditions. Its tradename, which suggests the presence of an enzyme, should be reconsidered.

14 Labeling Review
Labeling review and suggestions will be in an addendum to this review.

15 Recommendations
15.1 Approval, Approvable, Non-approval
It is recommended that Hyal's diclofenac gel be approvable for AK. Treatment duration should be 90 days.

15.2 Labeling Recommendations
It is recommended that the Applicant address the labeling comments in the addendum to this review.

15.4 Others
1. The Applicant is recommended to provide certain items which were supposed to form part of the original NDA submission:
    a) Photography of the phase 3 studies CT1101-03 and CT1101-04 (Appendix 16.4 of these studies).
    b) Tables on complete clearance of lesions by covariates (Tables 11.1-11.9 in

Integrated Summaries of Safety and Efficacy, vol 1.46).
c) Tables in the integrated report on safety data in actinic keratosis, ——— (Tables 14 and 18, vol 1.50).

2. For more informative labeling, an analysis contrasting the proportion of patients showing complete clearance of lesions (cumulative lesion number score=0) in the diclofenac group vs that in the vehicle group 30 days post-treatment should be presented for ***each*** MBA (major body area) for the three phase 3 studies, separately and combined.

/S/ 10-7-99

Hon-Sum Ko, M.D.

cc: NDA 21-005
HFD-540
HFD-540/CSO/White
HFD-540/CHEM/Decamp
HFD-540/PHARM/Reid
HFD-880/BIOPHARM/Tandon
HFD-880/MICRO/Vincent
HFD-540/MO/Walker/Ko
HFD-725/BIOMETRICS/Freidlin

10-18-99 /S/
/S/
/S/ 10/17/99

APPEARS THIS WAY
ON ORIGINAL