CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-005

MEDICAL REVIEW(S)

Medical Officer Review for NDA* 21-005

DDDDP#981903

OCT 17 1999

1 General Information

1.1 NDA submission number	21-005
1.2 Applicant identification	
1.2.1 Name	Hyal Pharmaceutical Corp
1.2.2 Address and telephone number	2425 Skymark Ave Mississauga, Ont. Canada L4W 4Y6
1.2.3 Name of company contact official	Patricia Anderson Director, Regulatory Affairs
1.3 Submission/review dates	
1.3.1 Date of submission	10/20/98
1.3.2 CDER stamp date	10/22/98
1.3.3 Date submission received by reviewer	11/3/99
1.3.4 Date review begun	12/2/98
1.3.5 Date review completed	10/7/99
1.4 Drug identification	
1.4.1 Generic name	Sodium diclofenac
1.4.2 Proposed trade name	Solarase™
1.4.3 Chemical name	2-{2,6 dichlorophenyl)amino} benzeneacetic acid monosodium salt
1.4.4 Molecular formula	$C_{14}H_{10}Cl_2NNaO_2$
1.4.5 Molecular weight	318.13
1.5 Pharmacologic Category	Non-steroidal antiinflammatory drug
1.6 Dosage form	Gel

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* Abbreviations used in this review: ADA=anti-diclofenac antibodies; AE=adverse event(s), AIS=area of involvement score; AK=actinic keratosis (keratoses), ANOVA=analysis of variance; ASA=acetylsalicylic acid; ASR=application site reaction; AUC=area under the curve; BL=baseline; BLC=baseline lesion count; BLS=baseline lesion severity; BSI=baseline severity index; CHF=congestive heart failure; CLNS= cumulative lesion number score, Cmax=maxmum plasma concentration; CMC=Chemistry/Manufacturing Controls; CRF=case report form(s), DMF=drug master file(s); ——— assay; ETRS=eczema type reaction score; FPS=Fitzpatrick skin (types); FTU=finger tip unit; FU=follow up; GII=global improvement index; HA=hyaluronic acid (hyaluronan); ——— ——— . *H. pylori=Heliobacter pylori*; IGII=investigator's global improvement index; IND=Investigational New Drug Application; ITT=intent-to-treat; LOCF=last observation carried forward; MBA=major body area(s); NDA=New Drug Application; NLNS=new lesion number score, NSAID= nonsteroidal antiinflammatory drug; ——— PK=pharmacokinetic(s); TLNS=target lesion number score, PG=prostaglandin; PGII=patient's global improvement index; PUT=provocative use test; ——— SCC=squamous cell carcinoma; SD=standard deviation; TTS=total thickness score; URI=upper respiratory tract infection; UV=ultraviolet; WO=washout.

1.7 Route of Administration Topical

1.8 Proposed Indication & Usage section "——— (sodium diclofenac) gel is indicated for the topical treatment of actinic keratoses."

1.9 Proposed Dosage & Administration section

———) gel is applied to lesions twice daily ——

——— Normally 0.5 g of gel ———— , is used on each 5 cm x 5 cm lesion site. The recommended duration of therapy is from ———to 90 days. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to 30 days following cessation of therapy. Lesions that do not respond to therapy should be

———

[ ]

1.10 Related Drugs The following approved NDAs for diclofenac sodium are listed in the COMIS system:

NDA 20-037 CIBA VISION CORP	VOLTAREN OPHTHALMIC SOL 0.1% TOPICAL
NDA 20-809 FALCON PHARMS	DICLOFENAC SODIUM OPHTHALMIC SOL 0.1% TOPICAL
NDA 19-201 NOVARTIS PHARMS	VOLTAREN TABLETS
NDA 20-254 NOVARTIS PHARMS	VOLTAREN XR TABLETS
NDA 20-607 SEARLE	ARTHROTEC DELAYED ACTION, ENTERIC COATED TABLETS

1.11 Material Reviewed

1.11.1 NDA volumes reviewed 1.1, 1.12, 1.45-1.84, 1.132-1.148

1.11.2 Amendments reviewed Submissions dated 1/18/99 (BZ), 2/17/99 (NC) 3/17/99 (SU), 3/36/99 (BZ), 5/21/99 (BZ) and 7/7/99 (BZ)

1.12 Regulatory Background

Studies in support of the indication in this NDA (actinic keratoses, or AK) were conducted under IND ——— This IND was submitted on 4/1/93 for ———

——— The following have been important interactions with the Agency relating to IND ———

Pre-IND meeting of 11/5/92	Discussion on the ———
Meeting of 5/11/93	Discussion of —— study
Meeting of 4/24/95	Discussion of the indication for AK
Pre-NDA meeting of 12/15/97	Discussion on the submission of NDA for the indication for AK

At the pre-IND meeting, the Agency had determined that the hyaluronic acid component in Hyal's diclofenac gel would not incur the combination policy. There was no formal End-of-Phase 2 meeting, but the Agency provided advice at the meeting of 4/24/95 on Hyal's development program for the indication AK. At the pre-NDA meeting, the Agency affirmed that the primary analysis for efficacy would be based on complete clearance of lesions at the 30-day post-treatment visit.

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3 Chemistry/Manufacturing Controls

The drug product has the following formulation:

	%w/w
Diclofenac sodium	3.0
Benzyl alcohol	—
Polyethylene glycol monomethyl ether —	—
Sodium hyaluronate	—
Purified water	—

In the formulation intended for marketing, the sodium hyaluronate is ——— ——— The earlier clinical studies with Hyal's diclofenac used gels containing hyaluronate ——— The phase 3 trials and two dermal safety studies used gels containing hyaluronate ———

In his review dated 7/20/99, the CMC Reviewer, Dr. B.V. Shetty, recommended a NOT APPROVABLE action because of the following deficiencies: (1) ——— (deficient DMF), (2) drug product (specifications for hyaluronate sodium), and (3) stability (development of color on storage at room temperature). The first two issues appear to have been resolved. The Applicant asserts that the color change may have been due to a ——— impurity in the raw material or its decomposition product, but the concentration of either was below the level of detection. The CMC reviewers question the validity of the assay methodology.

The proposed tradename, Solarase, suggests that the product is an enzyme. This should be reconsidered.

4 Animal Pharmacology/Toxicology

Diclofenac is a nonsteroidal antiinflammatory drug (NSAID). Pharmacodynamic effects of NSAIDs are believed to be due to the inhibition of cyclooxygenase and reduced prostaglandin E_2 (PGE_2) activity. NSAIDs have been studied as cancer chemoprevention agents, and experimental data on inhibition of angiogenesis by diclofenac with hyaluronan have been reported (e.g. colon). It has been postulated that hyaluronan may help in the topical delivery of diclofenac by more sustained release due to a depot effect. The mechanism of action in the treatment of actinic keratosis, however, is unknown.

The primary adverse effects of diclofenac observed preclinically and in humans are gastrointestinal, and related to its cyclooxygenase inhibition. Systemic toxicity has been well described in the label of oral diclofenac (see Section 10.6). However, Hyal's proposed topical formulation only provides low systemic availability. Chronic topical studies in minipigs resulted in very slight to well-defined erythema and/or scab formation. There is no evidence of mutagenicity, genotoxicity or developmental toxicity (Pregnancy Category B for oral formulations of diclofenac). In rats, toxic maternal effects were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Hyaluronan is a naturally occurring polysaccharide and a normal body component. Toxic effects have not been well documented.

The Pharm/Tox review has been completed by Dr. L. Reid initially with no definitive recommendations. Upon submission of more information by the Applicant, Dr. Reid has the following recommendation: "From a Pharm/Tox perspective, the NDA could be approved provided that the chemistry reviewer can confirm that there are no impurities or degradants present at concentrations

- a) greater than — of the bulk drug product; or
- b) greater than — of the drug substance in the drug product; or
- c) the Sponsor can demonstrate that impurities or degradants are present at less than or comparable levels in marketed diclofenac tables.

Furthermore, any impurities and/or degradants found at higher concentrations would need to be identified, tested for genotoxicity, and found to be nongenotoxic."

5 Microbiology

The Microbiology review is not yet available.

6 Human Pharmacokinetics/Pharmacodynamics

The Biopharm review has been completed by Dr. V. Tandon and she recommends approval. This review, however, is not yet available.

7 Human Clinical Experience

7.1 Foreign experience The product Solarase™ has not been marketed anywhere. Some of the clinical trials done with this product were conducted outside of the U.S. They will be presented in other sections of this review.

7.2 Post-Marketing Experience Although the product Solarase™ has been approved in Canada, the UK, Sweden, Italy, Germany and France, it has not been marketed as of to-date. ———————————————

Comment

8 Clinical Studies

8.1 Introduction

The clinical studies in support of this NDA are listed in the following Table.

Clinical Studies Using Hyal's Diclofenac Sodium 3%

Study No.	Site(s)	Sample Size (M:F)	Dose	Treatment Duration	Control	Design
Controlled						
CT1101-03	U.S.	118 (89:29)	3%, 0.5 Gm bid	90 d	vehicle	parallel, db, rand
CT1101-07	U.S.	111 (85:26)	3%, 0.5 Gm bid	90 d	vehicle	parallel, db, rand
CT1101-04	Canada	195 (142:53)	3%, 0.5 Gm bid	30 or 60 d	vehicle	parallel, db, rand
AK-CT1101-01	Australia	150 (89:61)	3%, 0.25 Gm bid	12 wk	vehicle	parallel, db, rand
ST-5101-AUS-01	Australia	130 (73:57)	3% , ? Gm bid	8-24 wk	vehicle	parallel, db, rand
Uncontrolled						
TDHA-AK-CDN -93-001	Canada	29 (22:8) 10 (4:6) vehicle	3%, 1 Gm bid 0%, 1 Gm bid	210 d ≤90 d	amended with vehicle arm after study completeion	open; vehicle arm added after study completion
ST5101-GRK-01	Greece	19 (11:8)	3%, 1 Gm bid	210 d		open
Clinical Pharmacology						
— 9500	U.S.	19 (2:17)	irritancy test	single application		healthy volunteers
— 9502	U.S.	116 (20:96)	sensitization test	9-application induction (3 wks) single challenge application		healthy volunteers
— 9503	U.S.	25 (9:16)	phototoxicity test	single application		healthy volunteers
— 9504	U.S.	27 (6:22)	photoallergenicity test	6-application induction (3 wks) single challenge application		healthy volunteers
— 0046	U.S.	108 (24:84)	sensitization test	9-application induction (3 wks) single challenge application		patients on stable oral NSAIDs
— 97-1619-70 (CT1101-09)	U.S.	205 (40:192)	sensitization test	9-application induction (3 wks) single challenge application		healthy volunteers
AT-2101-14 (CT1101-08)	U.S. & Canada	269	sensitization & irritancy test	single 48-hr application		patients previously exposed to 3% diclofenac gel for ≥48 hr
No number	U.S. & Canada	54	3%, ½ Gm bid (AK) 3%, 2 Gm qid —	7-day application		AK or — pts with previous dermal reaction to 3% gel
Bioavailability						
BIBRA 91/148/PL	U.K.	6 (2:4)	— gel	7d each	1% diclofenac (emulgel formulation)	2-way crossover, healthy volunteers
BP329 LAB	Canada	23 males	3% gel	6 d each	Voltarol 75 mg qd	2-way crossover, healthy volunteers
EP105	Canada	12 (4:8)	3% gel	7 d to compromised skin; 7 d to intact skin		2-way crossover, dermatitis patients
Non-AK Indications						
1.						
003-HA —	U.S.	70 (24:46)	3%, 0.5 Gm bid	12 wk		open
TDHA- — -AUS-92-001	Australia	49	3%, 0.5 Gm bid	8 wk	vehicle	parallel, db, rand
TDHA- — -AUS-92-002	Australia	75	3%, 0.5 Gm bid	8 wk	vehicle	parallel, db, rand
TDHA- — -CDN-92-002	Canada	16	3%, 0.5 Gm bid	8 wk	vehicle	parallel, db, rand
TDHA- — CDN-92-003	Canada	16	3%, 0.5 Gm bid	8 wk	vehicle	parallel, db, rand
2.						
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-2101-16	U.S./Canada	616 (198:218)	3%, 2 Gm qid	30 d	vehicle	parallel, db, rand
TDHA-PC-CDN-92-001-AR	Canada	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	Canada	69 (38:31)	3%, 2 Gm qid	7 d	vehicle	parallel, db, rand
TDHA- — -PA-AUS-93-002-LR	Australia	90 (32:58)	3%, ? frequency	7 d	vehicle	parallel, db, rand
AT-2101-PC-AST-93-001	Germany	111 (23:83)	3%, 2 Gm qid	7 d	Emulgel (CIBA)	crossover, 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	Canada	8 (3:5)	3%, 2 Gm qid	?	vehicle	parallel, db, rand

Db=double-blind, rand=randomized, AK=actinic keratosis, ———

The clinical pharmacology studies on dermal safety are discussed in Section 10.4.3.2. The studies on bioavailability are reviewed by Biopharm (see above and Section 10.4.3.1). Safety data from studies on non-AK indications will be addressed in Section 10.4.3.3. The controlled and uncontrolled studies on AK will be presented in this section. The phase 3 studies considered adequate and well-controlled by the Applicant to support the indication for AK are: CT1101-03, CT1101-04 and CT1101-07.

8.2 Indication #1 Actinic Keratosis

Actinic Keratosis (AK) lesions usually appear as red, scaly patches and may be precursors to squamous cell carcinoma (SCC) induced by excessive exposure to ultraviolet light. The lesions are usually found in sun-damaged skin in patients who are middle-aged or older, and primarily involve the face, scalp, ears and upper extremities of individuals with fair skin and light complexion. The major risk factors for developing AK are skin type I (Fitzpatrick classification), excessive sun exposure, and inadequate protection from ultraviolet (UV) radiation.

NSAIDs (non-steroidal anti-inflammatory drugs) have been used in the treatment of diverse cancers, including head and neck tumors (indomethacin) and colon cancer (aspirin). Restoration of specific elements of the immune system, e.g. prostaglandin synthesis and macrophage suppressor function, has been postulated to be their mechanism of action. The Applicant has developed a 3% diclofenac gel with — hyaluronic acid for the treatment of actinic keratosis. This NDA contains the studies in support of this indication.

8.2.1 Trial #1. United States Multi-Center Trial: A Randomized, Multi-Center, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of 3.0% Diclofenac in the Topical Treatment of Outpatients with Actinic Keratoses (CT-1101-03) [Conducted 7/11/95 – 1/30/96]

8.2.1.1 Objectives

Primary objective: to evaluate the efficacy of Hyal's topical 3% diclofenac gel formulation in the treatment of actinic keratoses.
Secondary objective: to assess the safety and tolerability of Hyal's topical 3% diclofenac gel formulation in actinic keratosis patients.
Alternative secondary objective: to assess patients for the presence of serum anti-diclofenac antibodies.

8.2.1.2 Design Randomized, placebo-controlled, multi-center, double-blind, parallel-group trial to study the efficacy and safety of 3% diclofenac gel in the treatment of AK, with 4 Investigator and two arms (active vs vehicle).

8.2.1.3 Protocol Overview

8.2.1.3.1 Population and Procedures

A sample size of 108 was planned. All participants were outpatients/new patients initially seen by the investigator or designate. Selection criteria were:

INCLUSION

- clinical diagnosis of 5 or more AK lesions contained in one to three 5 cm x 5 cm blocks in one or more of the selected Major Body Area(s) (MBAs): forehead, central face, scalp, back of hands, and arms
- male or female 18 years of age or older
- at baseline patient had no clinically significant medical problems based on physical examination, and/or blood and/or urine examination which could confound study results
- if female, the patient had to be post-menopausal for at least one year or have had a hysterectomy or tubal ligation or otherwise be incapable of childbirth, or practiced one of the following methods of contraception for at least two months prior to study entry: oral contraceptives, spermicide and barrier, intrauterine device, and had a normal menstrual flow within 35 days prior to study entry
- if female of child bearing age/potential patient had to have screened negative for serum β-HCG test
- patient had undergone a 60-day washout period from any disallowed medication (see exclusion criteria) prior to being randomized
- patient was willing and able to provide written informed consent

EXCLUSION

- patient had a known history of, or was suspected of having hypersensitivity to any of the ingredients of the active or placebo medications to be used in the study
- patient had previous or current history of allergies to aspirin (ASA) or other NSAIDs
- patient presented with a dermatological or related condition, including psoriasis, in the designated site which could alter the absorption, accumulation and metabolism of study medication
- patient was being treated with disallowed concomitant medications including masoprocol (Actinex®), 5-FU (Efudex®), etretinate (Tegison®), cyclosporine, retinoids, trichloroacetic acid/lactic acid/peel, and/or 50% glycolic acid peel
- patient was unwilling to undertake the wash-out period and discontinue for the duration of the study the use in the designated treatment area(s) of hyaluronan-containing cosmetics (Visible Youth®), Actinex®, Tegison®, or other disallowed medications which could confound study results
- patient was a female who was lactating, pregnant, or who was of child-bearing age but not using adequate contraception (physical, chemical, or hormonal) or not surgically sterile
- patient received another investigational drug or was enrolled in another investigational device study within the previous 60 days

WITHDRAWAL CRITERIA

- patient withdrew consent
- Investigator or Sponsor deciding that withdrawal was in the best interest of the patient, e.g., safety concern
- adverse event including hospitalization or acute disease conditions
- repeat clinically significant dermal adverse event upon re-introduction of study drug after 7-day interruption
- pregnancy or discontinuation of contraceptive measures in females
- protocol violation (took <75% of expected medication, missed 2 consecutive visits, used prohibited meds)
- lost to follow-up
- termination by Sponsor

Patients who withdrew would complete "Early Termination/End of Study Visit" and be reminded to return for follow-up visit.

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:

	Visit Number					
	1	2	3	4	5*	6
	Screen	Treatment Phase				Follow-up
Procedure	Day -6	1	30	60	90	30 d post
Informed consent	x					
Inclusion/exclusion	x					
Demographics	x					
Medical history/current condition	x	x	x	x	x	x
Physical examination	x				x	
Medication history	x					
Skin cancer history	x					
Blood work and urinalysis**	x				x	
Selection criteria	x					
Randomization		x				
Lesion count /baseline severity index		x				
Lesion photography		x	x	x	x	x
Lesion count and Inv global			x	x	x	x
Patient's global			x	x	x	x
Eczematous type reaction score			x	x	x	
Area of involvement score			x	x	x	
Concomitant medications		x	x	x	x	x
Adverse events		x	x	x	x	x
Dispense medication		x	x	x		
Diary/compliance			x	x	x	

*Visit 5 procedures were end-of-study procedures and were followed in early termination as well.
**Blood work included CBC, serum chemistry, and in appropriate females, pregnancy tests.

During study, a blood sample was also collected at the onset of any dermal site reaction (which required a 7-day interruption of study drug use). If the reaction persisted or returned upon re-introduction of the treatment, the treatment was permanently discontinued. Provided the dermal reaction had resolved by the post-treatment follow-up visit, the patient was eligible to participate in a 7-day open re-challenge to their randomized study medication at a new site, usually the inner upper arm [Provocative Use Test (PUT)], with test site scoring on days 1 and 7 of the testing. Blood samples were obtained prior to and after the 7-day re-exposure for antibodies to diclofenac. Concomitant medications were noted on days 1 and 7 and termination record completed on day 7.

The study medication lot number was WDD9 for the active and WDE8 for the placebo gel. The gel was to be applied at 0.5 Gm bid per treatment "block" (maximum daily dose of 3.0 g for 3 "blocks") for up to 90 days. Plastic vaginal applicators were adapted for use on the medication tubes. A demarcation was made on the applicator indicating when 0.5 Gm of gel had been expressed into it. Its plunger was then pushed in to express the gel onto the target "block". Every effort was to be made to apply the study medication at the same times during the day.

Comments

1. The protocol did not mention use of the applicator. Instead, the dose (0.5 Gm) was estimated to be one "Finger Tip Unit" (FTU) per "block". If patients consistently used the applicator, then the product should be marketed with the same applicator, with clear instructions regarding its use.
2. The protocol and consent forms do not address sun exposure. No patient instruction sheet has been presented. However, in the study report (p. 23), it is stated: "In the present study careful instructions were given to the patients to avoid sun exposure

throughout the investigation. This, in effect, could increase the spontaneous remission rate to above the previously described 5 to 10% over the 4 months of study exposure." If sun avoidance is part of the regime, then this ancillary measure becomes an integral part of the treatment program.

If all lesions completely resolved in any given treatment "block", application of the study medication was terminated in that specific "block". If all lesions in all "blocks" completely resolved, the patient was considered to have successfully completed the trial and could stop study drug. The patient would complete Visit 5 procedures and was to return 30 days later for post-treatment follow-up visit.

Concomitant medications There were agents thought to be possible confounders of the study but not mentioned in the exclusion criteria; these were added to the list of prohibited medications before initiation of the study. The complete list included acitretin, aluminum acetate, cortisone, cyclosporine, diclofenac, flumethasone, 5-fluorouracil, glycolic acid, hydrocortisone, isotretinoin, masoprocol, methotrexate, silicone, sunscreens, tretinoin, triamcinolone and trichloroacetic acid. In addition, (1) hyaluronan-containing cosmetics, such as Visible Youth™, were prohibited and, if being used, required a 60 day washout period prior to entry; and (2) cosmetics, including moisturizers, were not allowed on the dermal application "block(s)".

Compliance This was measured in two ways:

- weight of investigational medication used daily (*total grams used from all tubes for a given patient /total # of days) divided by expected use per day* x 100
- number of daily applications administered by the patient (*total # of applications/total # of days) divided by expected # of applications* per day x 100

8.2.1.3.2 Evaluability Criteria The study report uses only ITT analysis. All patients are considered as evaluable.

8.2.1.3.3 Endpoints

Efficacy Parameters

1. Quantitative lesion response: lesion counts

   Each treatment "block" was identified as Block 1, 2 or 3 in the case report form (CRF) and assigned a corresponding "block"-specific plastic grid. The plastic grid was placed on the designated "block" and lesions lying beneath were identified on the grid using a permanent colored marker. In each "block" the lesions were sequentially numbered. At Baseline, target lesions were marked with a "T" beside the lesion number. At all other visits, new lesions were marked with a "N" beside the its number. The marked plastic grid for each "block" was then superimposed on the corresponding CRF grid and lesion location/numbers transcribed onto the CRF.

- Target Lesion Number Score (TLNS) = lesion count of baseline identified lesions
- New Lesion Number Score (NLNS) = lesion count of new or emergent lesions
- Cumulative Lesion Number Score (CLNS) = TLNS + NLNS

2. Semi-quantitative lesion response: scales rated as follows -

- Baseline Severity Index (BSI): 0 - no AK lesions evident on tactile or visual evaluation; 1 - clearly visible lesions with mostly thin scales, which might be palpated; tactile evaluation revealed presence of underlying lesions; 2 - many visible, small lesions easily felt on palpation; most lesions of the moderately thick scale type; a few large, thick, rough scaly lesions might also be present; 3 - many thick, hypertrophic and/or florid actinic keratoses which were clearly visible and palpable with well-defined borders
- Investigator's Global Improvement Index (IGII):

  -2 -significantly worse: significantly more lesions, or majority of them ↑ in size, coarseness & scale thickness

  -1 -slightly worse: more lesions, or some lesions increased in size, coarseness, and thickness of scales

0 -no change
1 -slightly improved: some lesions cleared, scales decreased in thickness, but most lesions unchanged
2 -moderately improved: many lesions cleared and scales decreased in thickness
3 -significantly improved: majority of lesions absent and remaining scales barely perceptible on palpation
4 -completely improved: lesions cleared completely, adherent scaling plaques not evident on palpation, lesions no longer perceptible to touch, but slight pink or red foci might be visible at their sites

- Patient's Global Improvement Index (PGII): same scale as IGII

3. Photography. Each investigator was supplied with a [redacted] camera. Lesions were photographed at all visits except initial Screening, Visit 1.

The study report states that the **primary** efficacy endpoints were: for ITT/LOCF, TLNS = 0, proportion (%) of patients with zero scores in all MBAs at follow-up, CLNS = 0, proportion (%) of patients with zero scores in all MBAs at follow-up, PGII - proportion (%) of patients with "completely improved" scores at follow-up, IGII - proportion (%) of patients with "completely improved" scores at follow-up. The "follow-up" visit refers to the visit at 30 days post-treatment (day 120).

Comment The Applicant was told at the pre-NDA meeting that the Agency considered complete clearing of lesions as the primary variable. The Agency prefers the use of the proportion of patients achieving complete clearing of AK lesions (CLNS=0) 30 days post-treatment for the primary analysis. However, the time point for primary analysis was not clearly laid out in the protocol.

Safety Parameters

- AEs and serious AEs: Reports were based upon what was recorded in the diary card, from observation of, or direct communication with, the patient. The Investigator was requested to determine, without undue solicitation, whether the patient had experienced AEs or emergent medical conditions.
- Clinical lab tests: hematology, biochemistry, urinalysis
- Serum anti-diclofenac antibodies (ADA) by [redacted]
- Eczematous Type Reaction Score/Area of Involvement Score (ETRS/AIS): ETRS was a standardized patch test score to describe the severity of dermal reaction (indurated, vesicular, and/or bullous). The AIS was added to provide information about the location and spread of a given local reaction, should it occur.

ETRS scores:	0 - negative,
	± - questionable erythema not covering entire area
	1 - definite erythema
	2 - erythema and induration
	3 - vesiculation
	4 - bullous reaction
AIS scores:	1 - reaction localized to specific lesions
	2 - reaction localized to entire designated site
	3 - reaction extended beyond designated site

- Provocative Use Test (PUT) - see above

8.2.1.3.4 Statistical Considerations

The primary analyses for efficacy and safety were to be done on the intent-to-treat population. The procedure of forwarding the last available efficacy observation for lesion counts or GII scores was to be used. ANOVA was used to analyze continuous variables and the proportion of patients with TLNS=0 or CLNS=0 was to be contrasted

between treatment groups with the Logit model adjusted for center. Rank transformation was to be employed if the dataset departed excessively from normality.

A per protocol analysis was not performed.

Comment The Applicant chose data from the 30-day post-treatment follow-up for primary analysis. The time point of primary analysis was not specified in the protocol. The original protocol did not include analysis of data from day 120 (30 days post-treatment), but an amendment on 1/4/96 added analysis of such data. However, this was not stated to be the primary analysis.

Adverse event data were summarized and an exploratory analysis investigating the relationship between dermal AEs and drug compliance was done using the Logit model. Any demographic or descriptive variable for which the two treatment groups were statistically different was investigated as potential covariates.

Sample size estimation was based on a desired effect size (difference in lesion counts between treatment groups ÷ S.D.) of 0.54. With an α error probability of 0.05 and β error probability of 0.20, 54 patients per treatment group would be required.

Comment This calculation is not based on the rate of clearing of lesions, which is the preferred primary variable.

8.2.1.4 Study Results

The Investigators were:

John Wolfe, Jr., MD
Baylor College of Medicine
Department of Dermatology
1 Baylor Plaza
Houston, TX 77030

J. Richard Taylor, MD
Miami VA Hospital
Dermatology Center
1201 North West 16th St
Miami, FL 33125

Sewan Kang, MD
The U of Michigan Med Ctr
Department of Dermatology
1910 A Alfred Taubman
Health Care Center
Ann Arbor, MI 48109-0314

Eduardo Tschen, MD
Academic Dermatology Associates
1203 Coal SE, Suites B & C
Albuquerque, NM 87106

Comment The Investigators were qualified.

Enrollment per center was as follows:

	John Wolfe, Jr., MD	J. Richard Taylor, MD	Sewan Kang, MD	Eduardo Tschen, MD
Diclofenac	15	15	16	14
Vehicle	16	14	14	16

8.2.1.4.1 Disposition and Demographics

Patient Disposition

	Diclofenac	Vehicle
randomized	60	60
applied treatment	59*	59*
completed all study visits	45	51
"withdrawals"	14	8
• adverse events	8	4
• non-compliance	6	2
• withdrew consent	0	2

*Patient #4-014 (diclofenac) was lost to follow up and #02-004 (vehicle) had motor vehicle accident: both excluded after randomization without evidence of drug use.

The AE CRF dataset indicates that an additional 5 diclofenac patients had discontinuation due to adverse events: #1-009, 2-001, 2-012, 3-005 and 4-025 (see details in Section 8.2.1.4.3 on safety data). Except for #4-025, the discontinuations were within 3, 9, 11 and 0 days of visit 5 (end of treatment visit). For #4-025, visit 4 was missed as a result of AE discontinuation.

Comment All 5 patients should be added back to the AE database for discontinuations. There would have been 40 completing treatment and 19 withdrawals in the diclofenac group, with 13 of the 19 due to AE. There is a distinction between "completing treatment" and "completing all visits". Since those 5 patients had actual visits subsequent to discontinuation of treatment, they still yielded real data for efficacy analysis.

Baseline Demographics

		Diclofenac	Vehicle
Age	mean ± SD	65.4 ± 12.3	64.8 ± 10.6
	range	35-87	45-85
Sex	M:F	44:15	45:14
Race	Caucasian	59	58
	Hispanic	0	1
Skin color	Pale	10	10
	Fair	45	45
	Slightly dark	3	4
	Moderately dark	1	0
FPS	III	10	9
	II	36	36
	I	13	14
BSI	mild	21	18
	moderate	33	33
	severe	5	8

		Treatment "Blocks"**	Sum of Lesions	Treatment "Blocks"	Sum of Lesions
TLNS distribution	Forehead	30	162	24	147
	Central face	17	60	17	81
	Scalp	4	29	9	60
	Back of hand	17	84	14	67
	Arm	13	59	12	62
	Total	81	394	76	417

There are no significant differences between treatment groups in the above parameters.

Numbers of treatment "blocks" studied per patient are shown as follows:

	Diclofenac	Vehicle
Patients with one treatment "block"	27	32
Patients with two treatment "blocks"	25	21
Patients with three treatment "blocks"	7	6

Comment These figures are inconsistent with those in the Table on baseline demographics shown above (81 "blocks" for diclofenac and 76 for vehicle). They would have yielded 98 "blocks" (27x1+25x2+7x3) for diclofenac and 92 for vehicle

(32x1+21x2+6x3). Moreover, on page 125 of the report, it is indicated that the total number of "blocks" were 98 for diclofenac and 95 for vehicle.

Concomitant medications. The most commonly reported concomitant medications were ASA, ibuprofen, paracetamol and ranitidine. Their use was relatively well balanced between treatment groups. The use of sunscreens was not allowed. Interestingly, there were 6 patients with concomitant medication use of liquid nitrogen (3 per treatment group) for actinic keratosis.

Comment These 6 patients who used liquid nitrogen were actually protocol violators, as the protocol excluded use of medications that could possibly confound the study (diclofenac: #1-004, 1-009, 1-014; vehicle: #1-015, 1-018, 1-030). They were all in Dr. Wolf's center. Analysis without these 6 patients and assuming worst case scenario does not alter the conclusions obtained from this study (superiority of diclofenac vs vehicle for CLNS=0 at 30 days post-treatment, p=0.007).

Overall compliance. The following estimates were provided:

	Diclofenac	Vehicle
(Actual weight of medication used/expected use) x 100%	99.4	122.1
(Actual number of applications/expected number) x 100%	88.0	92.7

Comment The figures suggest somewhat lower numbers of applications than expected but the amount of gel per application was probably higher than what it should have been, especially in the vehicle group.

8.2.1.4.2 Efficacy

Primary Efficacy Variable

The primary efficacy variable for this review is the proportion of patients showing complete clearing of all lesions (CLNS) at the 30-day follow-up visit.

Proportion Of Patients Experiencing Complete Resolution Of Lesions At 30-d Follow-Up

		Proportion	p value
CLNS*	Diclofenac	27/58 (47%)	
	Vehicle	11/59 (19%)	<0.001
TLNS	Diclofenac	29/58 (50%)	
	Vehicle	12/59 (20%)	0.001

*CLNS=cumulative lesion number score, TLNS=target lesion number score

The mean duration of treatment to clear all lesions (CLNS) was 73.9 days for diclofenac (N=31) and 70.8 days for vehicle (N=15).

Comments

1. The proportion for complete clearing shows superiority of diclofenac over vehicle.
2. Significant difference between diclofenac and vehicle in the rate of complete resolution already occurred by the end of the treatment period. Thus, at the end of treatment (day 90), the rates of clearing were 24/58 (41%) for diclofenac and 13/59 (22%) for vehicle with CLNS (p=0.014); and the figures with TLNS were 24/58 (41%) for diclofenac and 14/59 (24%) for vehicle (p=0.023).
3. The above data using ITT analysis do not include all patients randomized (60 per group). There is a discrepancy in the numbers with CLNS=0 (diclofenac 27, vehicle 11) and those used in calculating the mean time to CLNS complete resolution (diclofenac 31, vehicle 15). It is possible that the difference may be due to recurrence or new lesions found at the 30 day post-treatment follow-up. Since there were 27/58 with CLNS=0 and 29/58 with TLNS=0 in the diclofenac group at the 30-day follow-up, it is

evident that at least two patients in this treatment group with target lesion clearance had new lesions 30 days post-treatment.

Secondary Efficacy Variables

Cumulative Lesion Number Score (CLNS) and Target Lesion Number Score (TLNS).

Lesion Counts

			Delta Baseline			
		Baseline (mean)	Day 30 (mean)	Day 60 (mean)	Day 90 (mean)	30-d FU (mean)
CLNS*	Diclofenac	6.7	-0.5	-2.4	-3.9	-5.1
	Vehicle	7.1	-2.1	-3.4	-4.3	-3.9
	p-value		0.017	0.122	0.960	0.009
TLNS	Diclofenac	6.7	-1.8	-3.0	-4.6	-5.3
	Vehicle	7.1	-2.2	-3.6	-4.5	-4.3
	p-value		0.274	0.347	0.788	0.019

*CLNS=cumulative lesion number score, TLNS=target lesion number score

New Lesion Number Score (NLNS). Although the diclofenac group had more new lesions developing early in the course of treatment, by the 30-day follow-up visit, this has reversed, as shown in the following Table:

		Baseline (mean)	Day 30 (mean)	Day 60 (mean)	Day 90 (mean)	30-d FU (mean)
NLNS*	Diclofenac	0	1.3	0.7	0.7	0.2
	Vehicle	0	0.1	0.2	0.1	0.3

*NLNS=new lesion number score

Global Improvement Indices (GII).

Distribution of IGII and PGII Scores

	Score	4	3	2	1	0	-1	-2	Total
IGII* Day 30	Diclofenac	0	12	6	13	13	8	3	55
	Vehicle	0	8	11	20	12	2	0	53
Day 60	Diclofenac	0	20	12	10	7	5	1	55
	Vehicle	1	14	14	13	11	1	0	54
Day 90	Diclofenac	24	11	5	7	5	5	1	58
	Vehicle	13	14	12	10	8	2	0	59
30-d FU	Diclofenac	27	17	3	6	3	2	0	58
	Vehicle	11	15	8	12	10	3	0	59
PGII* Day 30	Diclofenac	2	8	10	10	15	3	7	55
	Vehicle	0	7	12	19	14	1	0	53
Day 60	Diclofenac	1	17	6	16	9	2	4	55
	Vehicle	0	14	12	15	12	1	0	54
Day 90	Diclofenac	20	14	5	6	6	4	3	58
	Vehicle	10	16	15	7	10	1	0	59
30-d FU	Diclofenac	24	20	4	3	7	0	0	58
	Vehicle	10	10	17	8	9	5	0	59

*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. Significant differences could be discerned by the end of treatment (day 90) for "complete improvement". This further improved in the diclofenac group after that. It can best be illustrated in the following Table for "complete improvement":

	Day 90		Post-Treatment 30-d Follow-up	
	IGII	PGII	IGII	PGII
diclofenac	24/58 (41%)	20/58 (34%)	27/58 (47%)	24/58 (41%)
vehicle	13/59 (22%)	10/59 (17%)	11/59 (19%)	10/59 (17%)
	(p=0.014)	(p=0.018)	(p<0.001)	(p=0.001)

2. It is evident from the data that the vehicle group had 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, 13/59 (22%) of the patients given vehicle had no change or worsening by IGII and 14/59 (24%) by PGII; thus at least 76% of vehicle-treated patients had improvement, and the mean change in CLNS was -3.9, with a baseline count of 7.1 in that group (-55%).
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".
4. Parametric analyses of the global improvement indices corroborate those by dichotomization.

Lesion Counts by Major Body Areas (Treatment "Blocks") The following gives CLNS by treatment "blocks" using data from the study report:

CLNS by Major Body Area

	Diclofenac		Vehicle	
	Baseline (Mean)	30-d Follow-up (Mean)	Baseline (Mean)	30-d Follow-up (Mean)
MBA	N=81*	N=79	N=76	N=76
Forehead	5.4	0.8 (-85%)	6.1	2.8 (-54%)
Central Face	3.5	0.9 (-74%)	4.8	1.4 (-71%)
Scalp	7.3	1.5 (-79%)	6.7	2.1 (-69%)
Back of Hand	4.9	1.4 (-71%)	4.8	3.4 (-29%)
Arm	4.5	1.8 (-60%)	5.2	2.3 (-56%)

*N refers to the number of treatment "blocks", not patients; CLNS=cumulative lesion number score

Comments
1. As discussed above, there is a discrepancy of the total number of "blocks" treated and analyzed. In this Table, the treatment "block" number in the diclofenac group also changed (decreased from 81 to 79) between baseline and 30-d FU visit. It is possible that the decrease is due to missing data or lesion clearance in those "blocks".
2. 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	22/42 (52%)	11/43 (26%)	0.0127
Hand, Arm/Forearm	10/25 (40%)	4/22 (18%)	0.1099

Conclusion: Hyal's diclofenac gel was superior to vehicle for head and neck lesions. Efficacy on lesions on hands or arms/forearms have not been satisfactorily documented. Such an analysis would be useful information to be reflected in labeling.

Photography The photography data have not been presented. Appendix 16.4 of the study report is supposed to be photography of the typical responses.

Treatment-center effects There were no significant treatment-center interactions in the

primary analysis of data. The treatment effects were all in the same direction across centers.

8.2.1.4.3 Safety

The safety database is the ITT population minus patient #2-010, for whom the Applicant states that there are no safety data collected. The patient was dropped after 23 days of treatment for "noncompliance".

Comment The ITT population defined by the Applicant has already excluded two patients on the basis of lack of study medication use (one in each treatment group; see section 8.2.1.4.1). It is unclear why #2-010 should be excluded from safety database even though diclofenac had been used for 23 days.

Exposure

Mean duration of treatment was 74.7 days for the diclofenac and 79.5 days for the vehicle group. The mean total dose was 106.9 Gm for the diclofenac and 127.7 Gm for the vehicle group. The lower exposure to study medication in diclofenac group was due to the greater number of early terminations.

Comment The Applicant attempts to use the above exposure data to relate "compliance" to dermal AE and gives the following figures:

	"Compliant"	"Noncompliant"	
Presence of dermal AE	54/80 (68%)	29/36 (80%)	p=0.074

It has been concluded that compliance to the study regimen was influenced by presence of dermal adverse events. However, this relationship appears to be marginal. Moreover, compliance was also defined by other factors, including the use of prohibited medications and missing visits, which render any conclusion on its relationship with dermal AEs tenuous.

Adverse Events

AEs were reported in 52/58 (90%) and 48/59 (81%) of diclofenac and vehicle treatment groups, respectively. AE incidence is shown in the Table in Appendix III.

Comments

1. The most common adverse events were pruritus, "application site reaction" (ASR) and dry skin. The ASRs were not clearly defined by the Applicant. Some of the subjective manifestations have been classified under adverse events of the "nervous system" because of coding by the statistics contractor. Thus, "paresthesia" includes stinging, tingling, tingling/burning, burning/stinging, sting and itch, and prickly sensation. "Hyperesthesia" includes such terms as soreness, tenderness, sensitivity, sore, mild tenderness, and tender; and "tingling" includes tingling, and stinging. This has the effect of breaking up the incidence of the dermal adverse events, which makes evaluation difficult. Most of the events under "skin and appendages" and "nervous system" were considered to be at least possibly related to treatment. In addition, 4 diclofenac-treated patients developed conjunctivitis, lacrimation, or eye pain which were considered related. However, there has been no evidence of ocular toxicity in preclinical studies (see Pharm/Tox review).
2. The severity of most AEs were mild (72% of dermal events in diclofenac and 84% in vehicle group) or moderate ("mild or moderate" events being 96% and 97% of dermal AEs in the two treatment groups) and resolved completely with or without treatment interruption. Discontinuation was more frequent in the diclofenac group (see below).

Serious Adverse Events and Deaths

No deaths were reported. Four patients experienced serious AE, all considered *unlikely* to be related to treatment:

- Diclofenac 2: recurrence of basal cell carcinoma 1, pelvic injury 1.
- Vehicle 2: Motor vehicle accident and trauma 1, and squamous cell carcinoma 1.

Discontinuation due to Adverse Events

There were 13 patients in the diclofenac (see Section 8.2.1.4.1 "Disposition and Demographics") and 4 in the vehicle group who discontinued treatment because of adverse events:

Diclofenac	Vehicle
1-003 ASR#, rash, hypercholesterolemia	1-010 ASR, paresthesia, conjunctivitis
1-005 ASR, rash, pruritus, dry skin, photosensitivity reaction	1-024 ASR, rash, pruritus
1-017 vesiculobullous rash	2-009 pruritus, dizziness, headache, nervousness, urine frequency
1-023 ASR, rash, ulceration	2-011 pruritus
2-005 erythema, pruritus	
2-020 ASR, erythema, edema, paresthesia	
2-024 erythema, pruritus	
3-015 vesiculobullous rash, erythema, hyperesthesia	
1-009* ASR	
2-001* erythema, pruritus, edema	
2-012* erythema, pruritus, edema, ASR, asthenia, somnolence, migraine, dyspnea, eosinophilia, CPK increase	
3-005* pruritus, rash, erythema, hemorrhage, dry skin, exfoliation	
4-025* ASR, erythema	

*Five patients not included as "withdrawal due to adverse events" in study report because of discontinuation near visit 5;
#ASR=application site reaction.

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

The following Table gives the findings for ETRS/AIS. The distribution of ETRS/AIS with respect to the location of treatment "blocks" has not been provided.

	Diclofenac	Vehicle
ETRS*		
Questionable erythema	0	2
Definite erythema	23	7
Erythema and induration	12	0
Vesiculation	0	0
Bullous reaction	0	0
AIS		
Reaction localized to lesions	7	1
Reaction localized to site	16	8
Reaction extending beyond site	12	0

*ETRS=Eczematous Type Reaction Score, AIS=Area of Involvement Score

Provocative Use Test (PUT)

Data were not presented in this report but separately presented with PUT from other studies. See 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

Eighteen (18) patients had blood drawn pre-PUT for analysis for ADA (diclofenac 15, vehicle 3). Of 33 serum samples tested, evidence of antibodies to diclofenac was not detected.

8.2.1.5 Conclusions

1) In patients who used a 90-day regimen of 0.5 g bid per 5cm x 5cm application "block", topical diclofenac gel was superior to vehicle gel in the treatment of actinic keratosis lesions. Regional efficacy will be reflected in labeling.
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.

8.2.2 Trial #2. Canadian Multi-Center Trial: A Multicentre, Double-Blind, Placebo-Controlled, Randomized Study To Evaluate The Safety And Efficacy Of Topical 3% Diclofenac Gel (HYAL CT1101) In The Treatment Of Outpatients With Actinic Keratosis (CT-1101-04) [Conducted 8/3/95-2/6/96]

8.2.2.1 Objectives

Primary objective: to evaluate the efficacy of Hyal's topical 3% diclofenac gel formulation in the treatment of actinic keratoses
Secondary objective: to assess the safety and tolerability of Hyal's topical 3% diclofenac gel formulation in actinic keratosis patients.

8.2.2.2 Design Randomized, placebo-controlled, multi-center, double-blind, parallel-group study to evaluate the efficacy and safety of 3% diclofenac gel in the treatment of AK, with 6 Investigators and 4 arms: diclofenac for 30 days or 60 days vs vehicle for 30 days or 60 days respectively (to be referred to as d-30, d-60, v-30 and v-60 in this review) randomized at a ratio of 1:1:1:1.

Comment This trial is a variant of dose-ranging study (for duration). Ideally dose-ranging is to be completed in phase 2.

8.2.2.3 Protocol Overview

Other than the use of 4 treatment arms with dosing periods different from that in CT1101-03, this study had an almost identical protocol. Because of the differences in dosing periods, the final 30-day post-treatment visit would occur on day 60 for d-30 and v-30 groups and on day 90 for d-60 and v-60 groups. The following are differences between CT1101-04 and CT1101-03:

	CT11010-04	CT-1101-03
Treatment arms	diclofenac 30 days and 60 days vehicle 30 days and 60 days	diclofenac 90 days vehicle 90 days
Treatment "blocks"	scalp, face, forehead, back of hand*	scalp, face, forehead, arm, back of hand
Total thickness score	evaluated**	not evaluated
Histopathology	evaluated*** on 2 mm punch biopsies	no biopsies
Population for primary analysis	ITT and "efficacy subset" (protocol#)	ITT only
Hypothesis for sample size estimation	delta of 4 lesion counts from BL to FU# across treatment groups (i.e., v-30, v-60, d-30, d-60 with drop of 1, 1.3, 2.6 & 4 lesions respectively), with SD of 6.	effect size of 0.54 (i.e., difference in delta between treatment groups of 2.7, 3.3 or 3.8 lesions, with SD assumed to be 5, 6 or 7 respectively)

*forearms not included in protocol of CT1101-04, but some patient had such data collected. **Total thickness score (TTS) for each lesion scored as R=completely resolved, 0=visible but not palpable, 1=visible and palpable, 2=raised with visible scaling, 3=hyperkeratotic and >1 mm in height. ***Histopathology scored on biopsies with a 0-3 scale for hyperkertosis, parakeratosiss, atypia in follicular epidermis, elastosis, telangiectasis, and inflammation; and a 0-4 scale for atypia for non-follicular epithelium. #FU refers to 30-day post-treatment follow-up visit, BL=baseline. ##Per protocol analysis excludes patients who (1) missed 2 or more consecutive visits, (2) took disallowed concomitant medications, (3) used <75% of study medications and (4) had major treatment "block" identified as "arm".

The study medication lot numbers and application method were the same as in CT1101-03 gel (lot WDD9 for the active and WDE8 for the placebo).

8.2.2.4 Study Results

The Investigators were:

Jason Rivers, M.D.
University of British Columbia
Vancouver, BC

Neil Shear, M.D.
University of Toronto
Toronto, ON

Lyn Guenther, M.D.
Wellington Dermatology Associates
London, ON

John Arlette, M.D.
The Dermatology Center
Calgary, AB

Wayne Carey, M.D.
McGill University-RVH
Montreal, PQ

Yves Poulin, M.D.
Centre Dermatologique du Quebec
Metropolitain, Ste.-Foy, PQ

8.2.2.4.1 Disposition and Demographics

Patient Disposition

Enrollment and patient disposition per center were as follows:

Center+	1	2	3	4*	5*	6*	Total
Diclofenac-30 d	8	3	4	15	10	9	49
Vehicle-30 d	8	3	4	15	10	9	49
Diclofenac-60 d	8	2	4	15	10	9	48
Vehicle-60 d	8	3	4	15	10	9	49
Total randomized	32	11	16	60	40	36	195
Withdrawn	0	1	2	5	2	1	11
Completed	32	10	14	55	38	35	184

+Centers: 1=Rivers, 2=Shear, 3=Guenther, 4=Arlette, 5=Carey, 6=Poulin; *centers 4, 5, and 6 each had one enrolled patient not randomized because of not meeting enrollment criteria.

Reasons for withdrawal were:

	d-30*	v-30	d-60	v-60
Adverse event	2	1	4	1
Noncompliance	0	1	0	0
Consent withdrawn	1	0	0	0
Lost to follow-up	0	0	1	0
Total	3	2	5	1

*d-30=diclofenac 30 d, v-30=vehicle 30 d, d-60=diclofenac 60 d, and v-60=vehicle 60 d treatment groups.

Demographics

		d-30*	v-30	d-60	v-60
Age mean±SD		67±10	67±11	70±10	65±9
range		38-85	34-90	47-86	45-83
M:F		33:16	35:14	33:15	41:8
Skin color**	Pale	4	0	1	0
	Fair	7	9	5	2
	Slightly dark	35	35	30	38
	mod dark	3	5	12	9
Skin type	I	7	7	11	5
(Fitzpatrick)	II	23	35	28	36
	III	18	5	9	8
	IV	1	2	0	0
BSI	mild	24	28	29	28
	moderate	23	19	19	19
	severe	2	2	0	2
Treatment	Scalp	5 (6.6)	6 (6.5)	7 (5.6)	5 (8.4)
"blocks"	Forehead	29 (6.7)	30 (5.6)	31 (5.6)	35 (6.0)
(mean	Central face	14 (5.6)	18 (4.2)	19 (3.6)	13 (2.8)
number of	Back of hand	9 (7.6)	9 (6.7)	8 (7.0)	9 (7.9)
lesions)	Arm	0	2 (3.5)	1 (1.0)	1 (2.0)
	Total	57	65	66	63

*d-30=diclofenac 30 d, v-30=vehicle 30 d, d-60=diclofenac 60 d, and v-60=vehicle 60 d treatment groups. Racial data not shown above - all patients being Caucasian. **The only significant difference between groups was in skin color (p=0.006), due to the wider distribution in the diclofenac groups.

Comment The above Table shows that the treatment groups were comparable. Most of the treatment "blocks" were over the forehead, and approximately ¼ in the face, with the rest distributed between the scalp and hands. The distribution of patients treated with different numbers of treatment "blocks" was not presented. However, since the average was 1.3 treatment "blocks" per patient (see following Table), it would appear that most had only one "block" studied.

	d-30*	v-30	d-60	v-60	Total
Total number of treatment "blocks"	57	65	66	63	251
Total number of patients	49	49	48	49	195
Treatment "blocks" per patient	1.2	1.3	1.4	1.3	1.3

*d-30=diclofenac 30 d, v-30=vehicle 30 d, d-60=diclofenac 60 d, and v-60=vehicle 60 d treatment groups.

Treatment compliance

	d-30*	v-30	d-60	v-60
% expected weight used	125	113	106	110
% expected applications	92	91	89	95

*d-30=diclofenac 30 d, v-30=vehicle 30 d, d-60=diclofenac 60 d, and v-60=vehicle 60 d treatment groups.

Comment The figures suggest somewhat lower numbers of applications than expected but the amount of gel per application was probably higher than what it should have been.

The most commonly reported concomitant medications were ASA, acetaminophen, hydrochlorothiazide, nifedipine and lovastatin. Their use was relatively well balanced between treatment groups. The use of sunscreens was not allowed. There were also

patients who used liquid nitrogen, azathioprine, hydroxyurea, Retin-A, glycolic acid, and "procedure":

liquid nitrogen	d-30	#5016	unknown dose and date of use
	v-60	#4044	single treatment on 10/15/95
azathioprine	d-30	#4004	50 mg qd, together with prednisone 10 and 7.5 mg qd
	v-60	#2009	25 mg qd since 1972
hydroxyurea	v-60	#4010	500 mg tid since 1987, together with allopurinol 300 mg qd
Retin-A	v-60	#5024	0.1% qd between 12/93 to 9/95, together with prednisone and erythromycin
glycolic acid	v-60	#3008	topical application 12/19/95
"procedure"	d-60	#4001	radiation therapy from 8/1/95 with unknown dose daily
	d-60	#6028	laser CO_2 one dose on 10/19/95

Comment These 9 patients are actually protocol violators, as the protocol excludes use of medication that possibly confounds study results. However, these violations do not affect the conclusions to be reached. The two violators in the 30-day treatment group would not help in reversing the failure outcome of this regimen. For the 60-day treatment regimen, taking the worst case scenario by excluding the 2 diclofenac patients using these therapies and assuming them as successes (and similarly excluding the 5 vehicle patients and assuming them as failures), the outcome for the primary variable still shows superiority for diclofenac (CLNS=0 at post-treatment day 30 with p value of 0.045).

8.2.2.4.2 Efficacy

This review will use ITT as the primary analysis for efficacy. The study report's ITT population includes all randomized subjects. The per protocol analysis done by the Applicant has substantially fewer patients, and will not be presented here. The differences between the two populations are shown as follows:

	d-30*	v-30	d-60	v-60	Total
ITT population	49	49	48	49	195
Efficacy subset (per protocol)	40	38	37	33	148
Difference	9	11	11	16	47
Reasons:					
missed ≥2 consec visits	0	0	0	0	0
took prohibited med	0	0	0	0	0
< 75% use of med	9	9	10	15	43
Major "block" as arm	0	2	1	1	4

*d-30=diclofenac 30 d, v-30=vehicle 30 d, d-60=diclofenac 60 d, and v-60=vehicle 60 d treatment groups.

Comment Although the ITT population is supposed to include all randomized subjects, in fact, the Applicant only used subjects with available data (on lesion counts and TTS). Thus, the ITT patient numbers are as follows:

	d-30*	v-30	d-60	v-60
Baseline	49	49	48	49
Day 30 visit	49	49	45	47
Day 60 visit	N/A	N/A	47	49
30 days post-treatment	48	47	46	48

*d-30=diclofenac 30 d, v-30=veh 30 d, d-60=diclofenac 60 d, and v-60=veh 60 d treatment groups.

Primary Efficacy Variable

The primary efficacy variable for this review is the proportion of patients showing complete clearing of all lesions (CLNS) at the 30-day follow-up visit.

Proportion Of Patients Experiencing Complete Resolution Of Lesions At 30-d Follow-Up

	Group	Proportion @ 30 d post-treatment	*p* value	Group	Proportion @ 30 d post-treatment	*p* value
CLNS*	d-30	7/49 (14%)		d-60	15/48 (31%)	
	v-30	2/49 (4%)	0.2212	v-60	5/49 (10%)	0.0214
TLNS	d-30	7/48 (14%)		d-60	16/48 (33%)	
	v-30	2/49 (4%)	0.2104	v-60	5/48 (10%)	0.0126

*CLNS=cumulative lesion number score, TLNS=target lesion number score

The mean duration of treatment to clear all lesions (CLNS) was 29 days for both d-30 (N=7) and v-30 (N=2) groups; and 58 days for d-60 (N=15) and 48 days for v-60 (N=5) groups.

Comments

1. The proportion for complete clearing shows superiority of d-60 over v-60 but not d-30 over d-30. In fact, the only significant difference was between d-60 and v-60 at 30 days post-treatment. At no other time point was there significant difference between active and vehicle for either the 30-day or 60-day treatment regime.
2. The proportion achieving CLNS=0 for the v-60 group (5/49) was given as 8% in two places in the report. The Biometrics Reviewer has attempted to verify the information and found the figure in the above Table (10%) to be correct.
3. The mean time to CLNS=0 for the v-60 group is shown to be 53 days for 4 patients in the Summary Statistics Table on page 233 of the report (vol 1.70, p.235). This is in contrast to the data above (48 days in 5 patients; page 80 of report). However, this parameter is not a primary or secondary variable and will not affect the conclusions on this study.

Secondary Efficacy Variables

Cumulative Lesion Number Score (CLNS) and Target Lesion Number Score (TLNS).

Lesion Counts

			Baseline (mean)	Delta Baseline Day 30 (mean)	Day 60 (mean)	30-d FU (mean)
CLNS	d-30		7.6	-0.8		-3.9
	v-30		7.1	-1.3		-1.7
		p-value		0.6394		0.0079
	d-60		7.0	+0.1	-2.0	-3.8
	v-60		7.4	-1.4	-2.1	-1.7
		p-value		0.2784	0.9851	0.0138
TLNS	d-30		7.6	-2.5		-4.5
	v-30		7.1	-2.0		-2.4
		p-value		0.3204		0.0014
	d-60		7.0	-2.3	-3.5	-4.5
	v-60		7.4	-2.2	-2.8	-2.5
		p-value		0.9401	0.2837	0.0031

*CLNS=cumulative lesion number score, TLNS=target lesion number score

New Lesion Number Score (NLNS). An analysis of New Lesion Number Score (NLNS) was not provided with its overall score at different time-points. Rather, mean new lesion counts over each treatment "block" was presented, as shown in the following Table:

	Day 30				Day 60				30-d FU			
	scalp	forehd*	face	hand	scalp	forehd	face	hand	scalp	forehd	face	hand
d-30	1.6	1.4	0.4	3.1					0.8	0.4	0.4	0.9
v-30	1.2	0.6	0.2	0.7					1.3	0.8	0.1	0.1
d-60	0.3	2.2	0.6	4.1	0.3	0.8	0.4	4.4	0.6	0.5	0.0	0.6
v-60	0.0	0.5	0.2	2.0	0.0	0.3	0.1	2.4	0.0	0.6	0.3	1.6

*forehd=forehead; face=central face and hand=back of hand; at baseline NLNS=0, as scores are for new lesions.

Comment The active groups (d-30 and d-60) had higher mean counts of new lesions during treatment than the corresponding vehicle groups. This is consistent with the finding in CT1101-03 (Section 8.1.2.4.2). However, the reason is obscure. Additionally, the back of hand had more new/emergent lesions than other "blocks". It may be speculated that lesions on the hand are harder to treat because of contact, hand washing and other factors that may remove the drug from skin.

Total Thickness Score (TTS). The Applicant used resolution of TTS (TTS=0) as another primary parameter. This review treats it as secondary.

Proportion Of Patients Experiencing TTS Resolution (TTS=0) At 30-d Follow-Up

		Proportion	*p* value		Proportion	*p* value
TTS*	d-30	7/49 (14%)		d-60	12/48 (25%)	
	v-30	2/49 (4%)	0.2112	v-60	3/49 (6%)	0.0340

*TTS=total thickness score

Comment TTS is a non-validated endpoint summing the estimates of the thickness of individual lesions and is subject to variability because of dependence on the Investigator's visual and tactile senses and on the total number of lesions in a patient. Nevertheless, it corroborates the findings from CLNS and TLNS, showing superiority of active over vehicle only for the 60-day regime, and only at a sinlge time point: 30 days post-treatment. Its interim data also correspond to those of the lesion counts (CLNS and TLNS), and will not be further elaborated on here.

Global Improvement Indices (GII). The following data presented in the study report are without LOCF:

Distribution of IGII and PGII Scores

	Score	4	3	2	1	0	-1	-2	Total
IGII* Day 30	d-30	3	11	10	12	5	5	3	49
	v-30	0	14	8	13	12	2	0	49
	d-60	3	10	10	7	4	10	2	46
	v-60	2	11	10	14	6	4	0	47
Day 60	d-60	6	17	8	10	1	1	3	46
	v-60	7	11	8	15	5	2	1	49
30-d FU	d-30	8	22	11	4	2	1	0	48
	v-30	2	12	4	16	10	3	0	47
	d-60	15	16	6	8	1	0	0	46
	v-60	4	12	7	11	10	3	1	48
PGII* Day 30	d-30	2	12	17	2	6	6	4	49
	v-30	0	13	13	10	13	0	0	49
	d-60	2	12	7	11	4	5	5	46
	v-60	4	12	11	7	9	4	0	47
Day 60	d-60	7	16	10	10	1	0	3	47
	v-60	8	13	11	6	8	2	1	49
30-d FU	d-30	8	20	11	3	5	1	0	48
	v-30	1	12	8	13	13	0	0	47
	d-60	14	17	6	5	4	0	0	46
	v-60	4	20	6	6	10	2	0	48

*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

Parametric Analysis of IGII and PGII (Mean Scores)

	IGII*			PGII		
	Day 30	Day 60	30-d FU	Day 30	Day 60	30-d FU
d-30	1.4		2.5	1.4		2.4
v-30	1.4		1.4	1.5		1.4
p-value	0.2829		0.0027	0.3705		0.0291
d-60	1.2	2.0	2.8	1.2	2.1	2.7
v-60	1.5	1.8	1.6	1.6	1.9	2.0
p-value	0.8299	0.2981	0.0006	0.3734	0.3076	0.1121

*IGII=Investigator's global improvement index; PGII=Patient's global improvement index; FU=follow-up

Comments

1. Significant differences were not discerned by the end of treatment in the 30-day or the 60-day regimen for "complete improvement" but more patients had "complete improvement" 30 days post-treatment, such that the d-60 group showed superiority over v-60 by follow-up. This can best be illustrated in the following Table:

	Patients Showing "Complete Improvement"			
	End-of Treatment		Post-Treatment 30-d Follow-up	
	IGII	PGII	IGII	PGII
	Day 30		Day 60	
d-30	3/49 (6%)	2/49 (4%)	8/49 (16%)	8/49 (16%)
v-30	0/49 (0%)	0/49 (0%)	2/49 (4%)	1/49 (2%)
	(p=0.4451)	(p=0.6748)	(p=0.1344)	(p=0.1404)
	Day 60		Day 90	
d-60	6/48 (13%)	7/48 (15%)	15/48 (31%)	14/48 (29%)
v-60	7/49 (14%)	8/49 (16%)	5/49 (10%)	5/49 (10%)
	(p=0.8954)	(p=0.9642)	(p=0.0213)	(p=0.0269)

IGII=investigator's global improvement index, PGII=patient's global improvement index.

2. It is evident from the data that the vehicle group had 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, 13/47 (28%) of the v-30 and 14/48 (29%) of the v-60 groups had no change or worsening by IGII. Thus at least 71% of vehicle-treated patients had improvement, and the mean change in CLNS was -1.7 (baseline 7.1; -24%) in the v-30 and -1.7 (baseline 7.4; -23%) in the v-60 groups. Findings by PGII corroborated the IGII data.
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". However, at the end of treatment, both d-60 and v-60 groups showed more "complete improvement" with PGII.
4. The parametric analyses for both IGII and PGII show that even the 30-day treatment regime with diclofenac had been superior to vehicle, when evaluated 30 days post-treatment. This is not surprising, as such analyses have greater power. In addition, the parametric analysis for PGII has given results in contrast to those from dichotomization for "complete improvement", and from analyses of CLNS=0 or TLNS=0 at 30 days post-treatment, by showing superiority of d-30 vs v-30 but not d-60 vs v-60. The reason for this difference is obscure.

Lesion Counts by Major Body Areas (Treatment "Blocks") The following gives CLNS by treatment "blocks" using data from the study report:

CLNS by Major Body Area

	Baseline				Day 30			
	scalp	forehd*	face	hand	scalp	forehd	face	hand
d-30	6.6	6.7	5.6	7.6	6.2 (- 6%)	6.0 (-10%)	3.4 (-39%)	9.3 (+22%)
v-30	6.5	5.6	4.2	6.7	5.7 (-12%)	4.5 (-20%)	3.2 (-24%)	5.8 (-13%)
d-60	5.6	5.6	3.6	7.0	3.6 (-36%)	6.0 (+ 7%)	2.7 (-25%)	9.6 (+37%)
v-60	8.4	6.0	2.8	7.9	5.0 (-40%)	4.5 (-25%)	2.6 (- 7%)	7.4 (- 6%)

	Day 60				30-d FU			
	scalp	forehd	face	hand	scalp	forehd	face	hand
d-30					3.8 (-42%)	2.9 (-57%)	2.5 (-55%)	5.1 (-33%)
v-30					5.7 (-12%)	4.5 (-20%)	3.2 (-24%)	3.8 (-43%)
d-60	2.3 (-59%)	3.6 (-36%)	2.0 (-44%)	9.7 (+39%)	2.3 (-59%)	3.2 (-43%)	1.1 (-69%)	4.0 (-43%)
v-60	2.6 (-69%)	4.1 (-32%)	2.3 (-18%)	7.8 (- 1%)	3.4 (-60%)	4.8 (-20%)	2.4 (-14%)	7.1 (-10%)

*forehd=forehead; face=central face and hand=back of hand; CLNS=cumulative lesion number score.

Comments
1. The above data were obtained without carrying forward information for missing visits. No statistical tests were performed by the Applicant on these data.
2. Data from the 4 treatment "blocks" for arm lesions (a protocol violation to treat arm lesions) are not included. Mean values for CLNS can be shown as follows:

	Baseline	Day 30	Day 60	30-d FU
d-30	0	0		0
v-30	3.5*	3.5		1.0
d-60	1.0	1.0	1.0	1.0
v-60	2.0	2.0	2.0	2.0

*d-30 had no arm "blocks" treated; data for v-30, d-60 and v-60 from 2, 1 and 1 "blocks" respectively.

3. The Applicant submitted an analysis of the data on clearance of lesions by anatomical location upon request (combined data of 30- and 60-day treatments):

	Proportion of patients with CLNS=0 at 30 days Post-Treatment Follow-Up (LOCF)		
Location	Diclofenac	Vehicle	p-value
Head/Neck	22/84 (26%)	6/85 (7%)	0.0017
Hand, Arm/Forearm	2/18 (11%)	2/20 (10%)	0.9113

Conclusion: Hyal's diclofenac gel was superior to vehicle for head and neck lesions. Since inclusion of arm/forearm lesions for study was a protocol violation, the data on hand/arm/forearm were derived primarily from hand lesions (see comment 2). An analysis on lesion clearance for the hands should be useful information to be reflected in labeling.

Histopathology Punch biopsies were done at screening visit and at the end of treatment at lesion #1 of treatment "block" #1. The following parameters were scored: hyperkeratosis, parakeratosis, atypia (epidermal and follicular), elastosis, telangiectasia and inflammation. There was a reduction of hyperkeratosis, parakeratosis and atypia in both active- and vehicle-treated groups, but no significant differences between groups.

Comment Since biopsy was done at the end-of-treatment visit and not the 30-day follow-up visit, these could not be correlated with the primary endpoint data (CLNS 30 days post-treatment).

Photography The photography data have not been presented. Appendix 16.4 of the study report is supposed to be photography of the typical responses with 3 scenarios involving complete resolution - simple complete resolution (#1016), with irritant reaction (#1023) and with ETR (#5001).

Treatment-center effects The Applicant stated that the statistical model already included treatment x center interaction and that the individual by-center data have been presented in the summary efficacy Tables.

Comment The summary Table data for the centers are presented as pooled data of all 4 treatment groups per center. Moreover, these Tables do not include a presentation of the analysis of center effect for the primary efficacy parameter (proportion of patients with CLNS=0). The Biometrics Reviewer recognises this and has included center effect in her analysis of the statistical data.

8.2.2.4.3 Safety

The safety database is the ITT population of 195 patients.

Exposure

	d-30	v-30	d-60	v-60
Mean duration of treatment (days)	30	30	61	58
Mean number of treatment "blocks"	1.2	1.3	1.4	1.3
Expected use* (Grams)	36	39	85	75
Median total dose (Grams)	45	44	103	94
Mean total dose (Grams)	53	53	112	101

*based on the amount to be used per "block" = 0.5 Gm bid

Comment There was generally overuse of medication, but the Applicant attributes this as being skewed by outliers, as the median values were closer to expected.

Adverse Events

Adverse events were reported in between 79% to 92% of patients in different treatment

groups.

	d-30	v-30	d-60	v-60
Rate of AE*	41/49 (83%)	40/49 (82%)	38/48 (79%)	45/49 (92%)

*based on patients with at least one adverse event

The Incidence of adverse events is given in the Table in Appendix IV.

Comments

1. As in Study 1101-03, the majority of adverse events were reported for dermal reactions (pruritus, rash, dry skin and application site reactions (ASRs). The ASRs were not clearly defined. Some of the subjective manifestations have been classified under adverse events of the "nervous system" because of coding: paresthesia (burning, stinging, tingling, tickle, cool sensation) and hyperesthesia (soreness, tenderness).
2. Most of the adverse events were mild or moderate and their numbers were comparable across the active and vehicle arms. It is stated in the report (p. 119) that there were 10 "severe" adverse events in 7 patient (3 in d-30 and 7 in d-60 groups). However, this is contradicted by the Table in page 291 where only 5 patients are given as having had "severe" AEs (see following Table). A review of the Data Listings reveals 6 patients and 9 events. These events included tingling, alopecia, contact dermatitis, edema, rash and pruritus. The majority of AEs resolved completely without actions taken.

Severity	d-30	v-30	d-60	v-60
mild	27/49 (55%)	30/49 (61%)	24/48 (50%)	31/49 (63%)
moderate	9/49 (18%)	6/49 (12%)	7/48 (15%)	11/49 (22%)
severe	1/49 (2%)	0 (0)	4/48 (8%)	0 (0)
Total	37/49 (76%)	36/49 (73%)	35/48 (73%)	42/49 (86%)

3. Generally patients on active treatment had more adverse events categorised as "related" to treatment except for pruritus, which was both reported more frequently in the vehicle groups and considered "related" more frequently. However, it is probably more conservative to consider all dermal events together with paresthesia/ hyperesthesia "related", unless the occurrence is distant from a treatment "block".

Serious Adverse Events and Deaths

No deaths were reported. Four patients experienced serious AE, all considered *unknown* or *unlikely* to be related to treatment:

- Patient 5019 (v-30) *basal cell carcinoma*
- Patient 2010 (v-30) *angina pectoris*
- Patient 6001 (v-30) *HIV+*
- Patient 1020 (v-60) *squamous cell carcinoma (SCC)*

There were 3 additional significant adverse events considered *unlikely* related to treatment:

- Patient 3001 (v-30): *basal cell carcinoma*
- Patient 5011 (v-60): *basal cell carcinoma*
- Patient 1021 (d-60): *conjunctivitis*

Discontinuations due to Adverse Events

There were 8 patients who discontinued treatment because of adverse events, which were all application site reactions, including local irritation, rash and pruritus. Three of the 8 cases were "contact dermatitis": irritant (#4001), allergic (#2007) and unclassifed (#5001), all in the d-60 group.

	d-30 (N=49)	v-30 (N=49)	d-60 (N=48)	v-60 (N=49)
Discontinued	2	1	4	1
Patient IDs	#3012 ASR*	#4041 ASR	#2007 CD	#5024 ASR
	#6008 ASR*		#3002 ASR	
			#4001 CD	
			#5001 CD	

ASR=application site reaction, CD=contact dermatitis. *Patients 3012 and 6008 are given in the study report as withdrawn due to AE, but data listings (vol 1.74, p.159 and 173) do not indicate stopping treatment; patients probably discontinued at first treatment visit (day 30) which was also end-of-treatment visit for the d-30 group.

Comment Evidence of the "allergic" component of #2007's contact dermatitis has not been provided.

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

The following Table gives the distribution of patients with ETRS/AIS with respect to the location of treatment "blocks", and the mean scores for ETRS/AIS.

	d-30 (N=49)	v-30 (N=49)	d-60 (N=48)	v-60 (N=49)
Scalp	0	0	0	0
Forehead	6 (12%) [1.4] {2.3}	3 (6%) [1.0] {1.3}	9 (19%) [1.8] {2.3}	3 (6%) [0.2] {2.6}
Face	3 (6%) [2.4] {2.1}	1 (2%) [2.0] {2.0}	2 (4%) [1.3] {2.0}	1 (2%) [0.5] {3.0}
Back of hand	3 (6%) [2.0] {1.5}	0	4 (8%) [2.2] {2.0}	2 (4%) [1.0] {2.5}
Total	12 (25%)	4 (8%)	15 (31%)	6 (12%)

ETRS: 0.5=Questionable erythema, 1=Definite, 2=Erythema and induration, 3=Vesiculation, 4=Bullous reaction; AIS: 1=Reaction localized to lesions, 2=Reaction localized to site, 3=Reaction extending beyond site; mean ETRS given between [ ] and AIS between { }.

Comment The active groups appear to give more severe reaction than the vehicle groups, but the overall pattern of spread as shown by AIS was variable. The ETRS/AIS does not include the subjective symptoms (pruritus, tingling, burning), and is therefore incomplete information. Moreover, the Applicant admits that the identification of ETR was at the discretion of the Investigator and the criteria applied might have varied across centers.

Provocative Use Test (PUT)

Data for PUT were not included in this report but combined with those from other studies as a separate presentation. See 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

Eighteen (191) of the 195 patients had 2 samples of blood drawn for analysis for ADA. Evidence of antibodies to diclofenac was not detected.

8.2.2.5 Conclusions

1) This study demonstrates effectiveness of Hyal's 3% diclofenac gel used bid for 60 days in the treatment for AK lesions, but not when used for 30 days.
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.

8.2.3 Trial #3. A Randomized, Single Center, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of 3.0% Diclofenac Gel in Hyaluronan (SOLARASE®) in the Topical Treatment of Outpatients with Actinic Keratoses (CT-1101-07) [Conducted 3/4/96 – 11/31/96]

8.2.3.1 Objectives

Primary objectives: (1) to evaluate the efficacy of Hyal's topical 3% diclofenac gel formulation in the treatment of actinic keratoses and (2) to assess the safety and tolerability of Hyal's topical 3% diclofenac gel formulation in actinic keratosis patients.

Exploratory secondary objectives: (1) to assess patients for the presence of serum anti-diclofenac antibodies; and (2) to assess serum diclofenac levels after study drug had been discontinued upon completion of the dosing portion of the study (*post hoc*).

8.2.3.2 Design Randomized, placebo-controlled, single-center, double-blind 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 This single-center study adds safety information for patients treated for 90 days with the drug product.

8.2.3.3 Protocol Overview

8.2.3.3.1 Population and Procedures

A sample size of 108 was planned. All participants were outpatients/new patients initially seen by the investigator or designate. Selection criteria were:

INCLUSION

- clinical diagnosis of five or more AK lesions contained in one to three 5 cm x 5 cm blocks in one or more of the selected MBAs, the five MBAs being forehead, central face, scalp, back of hands, and arms.
- male or female 18 years of age or greater
- at baseline patient had no clinically significant medical problems based on physical examination, and/or blood and/or urine examination which could confound study results
- if female, the patient had to be post-menopausal for at least one year or had a hysterectomy or tubal ligation or otherwise be incapable of childbirth, or had practiced one of the following methods of contraception for at least two months prior to study entry; oral contraceptives, spermicide and barrier, intrauterine device, and had a normal menstrual flow within 35 days prior to study entry
- if female of child bearing age/potential patient had to have screened negative for a urine pregnancy test
- patient had undergone a 60-day washout period from any disallowed medication (see exclusion criteria) prior to being randomized
- patient was willing and able to provide written informed consent

EXCLUSION

- patient had a known history of, or was suspected of having hypersensitivity to any of the ingredients of the active or placebo medications to be used in the study
- the patient had previous or current history of allergies to ASA or other NSAIDs
- patient presented with a dermatological or related condition, including psoriasis, in the designated site which could alter the absorption, accumulation and metabolism of the study medication
- patient was being treated with disallowed concomitant medications including masoprocol (Actinex®), 5-FU (Efudex®), etretinate (Tegison®), cyclosporine, retinoids, trichloroacetic acid/lactic acid/peel, and/or 50% glycolic acid peel
- patient was unwilling to undertake the wash-out period and discontinue for the duration of the study the use in the designated treatment area(s) of hyaluronan-containing cosmetics (Visible Youth®), Actinex®, Tegison®, or other disallowed medications which could confound the study results
- patient was a female who was lactating, pregnant, or not using adequate contraception (physical, chemical, or hormonal), if not surgically sterile

- patient received another investigational drug or was enrolled in another investigational device study within the previous 60 days

Eligible patients were randomized in a 1:1 ratio to active diclofenac gel or vehicle. The study consisted of 3 phases: screening, treatment, and follow-up:

	Visit Number					
	1	2	3	4	5*	6
	Screen	Treatment Phase				Follow-up
Procedure	Day -6	1	30	60	90	30 d post
Informed consent	x					
Demographics	x					
Medical history/current condition	x	x	x	x	x	x
Physical examination	x				x	
Blood work and urinalysis**	x				x	
Selection criteria	x					
Randomization		x				
Lesion count /baseline severity index		x				
Lesion photography		x	x	x	x	x
Lesion count and Inv global			x	x	x	x
Patient's global			x	x	x	x
Eczematous type reaction score			x	x	x	x
Area of involvement score			x	x	x	x
Concomitant medications	x	x	x	x	x	x
Adverse Events			x	x	x	x
Dispense medication		x	x	x		
Diary/compliance			x	x	x	

*Visit 5 procedures were end-of-study procedures and to be followed in early termination as well.
**Blood work included CBC, serum chemistry, and in appropriate females, pregnancy tests.

In all patients, blood was taken prior to entry and at or around End of Treatment (Visit 5) for antibodies to diclofenac. Blood sampling for ADA and PUT was the same as in CT1101-03.

The study medication was to be applied at 0.5 Gm bid per treatment "block" (maximum daily dose of 3.0 g for 3 "blocks") for up to 90 days. Plastic applicators were adapted for use on the medication tubes. The applicator was placed over the tube mouth and the tube squeezed expressing gel into the applicator, pushing back the plunger. A pre-applied mark on the applicator indicated when 0.5 g of gel had been expressed into the applicator. The "loaded" applicator was removed from the tube and positioned above the treatment area where the plunger was depressed to express the gel. If patients were not able to use the applicator, they could use a finger-tip unit (an amount the size of the end of their index finger). It is not known how many patients actually used or preferred this approach. Every effort was to be made to apply the study medication at the same times during the day.

If all lesions completely resolved in any given treatment "block", application of the study medication was terminated in that specific "block". If all lesions in all "blocks" completely resolved, the patient was considered to have successfully completed the trial and could stop the study drug. The patient would complete Visit 5 procedures and was to return 30 days later for Follow-up visit.

Concomitant medications In the case of agents thought to be possible confounders of the study but not mentioned in the exclusion criteria, their exclusion was decided upon case by case. For instance,

(1) Sunscreen was not to be used on the treatment block(s), but patients might use it on other areas;
(2) Hyaluronic acid- (HA) containing cosmetics, such as Visible Youth™, were prohibited and, if previously used, required a 60 day washout period prior to entry;
(3) Cosmetics, including moisturizers, were not allowed on the dermal application block(s).

All medications used were recorded in the CRF with the exception of sunscreens, which were solicited separately in a telephone interview after completion of the study. The diary recorded any use of, or change in the use of, concomitant medications.

Compliance This was measured in two ways:

- weight of investigational medication used daily, (*total grams used from all tubes for a given patient/total # of days) divided by expected use per day* x 100
- number of daily applications administered by the patient (*total # of applications/total # of days) divided by expected # of applications* per day x 100

8.2.3.3.2 Evaluability Criteria See section 8.2.3.3.5 re: per-protocol analysis.

8.2.3.3.3 Endpoints

Efficacy Parameters

1. Quantitative lesion response: lesion counts

- Target Lesion Number Score (TLNS) = lesion count of baseline identified lesions
- New Lesion Number Score (NLNS) = lesion count of new or emergent lesions
- Cumulative Lesion Number Score (CLNS) = TLNS + NLNS

2. Semi-quantitative lesion response: scales rated as in Studies CT1101-03 and CT1101-04 –

- Baseline Severity Index (BSI)
- Investigator's Global Improvement Index (IGII) and
- Patient's Global Improvement Index (PGII)

The primary variables were (a) change from baseline at follow-up in TLNS and CLNS, and (b) proportion of patients with TLNS=0, CLNS=0. The secondary variables were (a) PGII scores and (b) IGII scores at follow-up.

Comment In the original protocol, the primary parameters were lesion counts (TLNS and CLNS) and PGII. IGII was regarded as a secondary parameter. In the study report, both global indices are now regarded as secondary. The Applicant has been told at the pre-NDA meeting that the Agency considers complete clearing of lesions as the primary variable.

Safety Parameters

AEs/serious AEs, hematology, biochemistry, urinalysis

Other Non-Efficacy Parameters

- Serum anti-diclofenac antibodies [ADA] by ———————
- Eczematous Type Reaction Score/Area of Involvement Score (ETRS/AIS): ETRS was a standardized patch test score to describe the severity of dermal reaction (indurated, vesiculous, and/or bullous). The AIS was added to provide information about the location and spread of a given local reaction, should it occur. See section

8.2.1.3.3 for scoring of these parameters (same as in CT1101-03).
- Provocative Use Test (PUT) - See section 8.2.1.3.1 (same as in CT1101-03).
- Serum diclofenac levels post treatment by ————

8.2.3.3.4 Statistical Considerations

The primary population for efficacy and safety analyses was the intent-to-treat group. The procedure of forwarding the last available efficacy observation for lesion counts or GII scores was used. ANOVA was used to analyze continuous variables and proportions were evaluated by *chi* square. Rank transformation was to be employed if the dataset departed excessively from normality. The time point for primary analysis is the 30-day post-treatment visit.

A per protocol analysis was performed including evaluable patients who did not (1) miss two or more consecutive visits or (2) take disallowed medications on two or more occasions. After completion of the study, an additional criterion for evaluability was added *post hoc*: administration of 75% or less of the expected dose of study drug on a per daily basis over the period of study drug administration.

Comment Since the primary analysis is on the ITT population, this change is not expected to influence decision making in this review.

Safety data were analyzed for *within* group differences using Wilcoxon Signed Rank Test and *between* group contrasts using ANOVA. Any demographic or descriptive variable for which the two treatment groups were statistically different was investigated as potential covariates.

As an exploratory analysis to determine the extent of diclofenac remaining in the circulating serum after stopping therapy, blood taken for ADA detection at the end of treatment was tested by ———— the serum diclofenac levels plotted against time since last dose.

The Applicant estimated sample size by using a desired effect size (difference in lesion counts between treatment groups ÷ S.D.) of 0.54. With an α error probability of 0.05 and β error probability of 0.20, 54 patients per treatment group would be required.

Comment This calculation is not based on the rate of clearing of lesions, which is the preferred primary variable.

8.2.3.4 Study Results

The Investigators were: James Del Rosso, DO/Dr. Kevin Welch, MD
West Florida Clinical Research Center
8333 North Davis Highway
Pensacola, Florida USA 32514

Comment Drs. Rosso and Welch were qualified.

8.2.3.4.1 Disposition and Demographics

Patient Disposition

	Diclofenac	Vehicle
enrolled	56	56
applied treatment	56	55
completed all study visits	44	49
"withdrawals"	12#	7#
• adverse events	8	3
• non-compliance	1	1
• withdrew consent	1	0
• lost to Follow-up	2*	3**

#12 additional patients in diclofenac and 1 in vehicle group also discontinued treatment due to AE but not considered "withdrawn" as they completed the 30-d post-treatment visit; including these would raise "withdrawal" numbers to 24 and 8 for diclofenac and vehicle respectively; *both having complete clearance of all lesions; **including one lost to follow up before first dose

Comment In section 12.2.3 of the study report (vo.1.77, p.88), there were 13 additional diclofenac patients who discontinued treatment due to adverse events (but not classified as "withdrawn") instead of 12.

Baseline Demographics

		Diclofenac		Vehicle		p-value*
Age	mean ± SD	64.3 ± 8.6		67.8 ± 8.3		0.038
	range	40-80		48-84		
Sex	M:F	38:18		47:8		0.029
Race	Caucasian	56		55		
Skin color	Fair	42		45		
	Slightly dark	12		9		
	Moderately dark	2		1		
FPS	IV	7		3		
	III	15		18		
	II	21		24		
	I	13		10		
BSI	mild	31		37		
	moderate	20		18		
	severe	5		0		
		Treatment "Blocks"**	Mean no. of lesions	Treatment "Blocks"	Mean no. of lesions	
TLNS distribution	Forehead	20	9.2	21	7.9	
	Central face	6	10.7	8	8.8	
	Scalp	6	11.2	4	8.8	
	Back of hand	17	9.0	16	8.0	
	Arm	9	6.1	6	7.2	

*P-values given here only if ≤0.05

**Treatment "blocks" in excess of 56 for diclofenac group because 2 patients had more than one treatment "block" (#018 - left and right arm and #110 - hand and arm).

Patients were well matched across treatment groups except for age and sex distribution (see above Table), as well as mean baseline lesion counts (9.2 in diclofenac group vs 8.0 in Vehicle group, p=0.032; not shown in above Table). The most commonly reported concomitant medications were ASA, acetaminophen, atenolol, digoxin, estrogen, hydrochlorothiazide (with or without triamterene), multivitamins, and

simvastatin. Their use was relatively well balanced between treatment groups. Five patients used sunscreens, all on the head (diclofenac 2, vehicle 3).

8.2.3.4.2 Efficacy

Primary Efficacy Variable

The primary efficacy variable for this review is the proportion of patients showing complete clearing of all lesions (CLNS) at the 30-day follow-up visit.

Proportion Of Patients Experiencing Complete Resolution Of Lesions At 30-d Follow-Up

		Proportion	p value
CLNS*	Diclofenac	18/53 (34%)	
	Vehicle	10/55 (18%)	0.061
TLNS	Diclofenac	18/53 (34%)	
	Vehicle	11/55 (20%)	0.102

*CLNS=cumulative lesion number score, TLNS=target lesion number score

The mean duration of treatment to clear all lesions was 62 days for diclofenac and 80 days for vehicle.

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. The difference between diclofenac and vehicle in the rate of complete resolution occurred primarily after the treatment period. Thus, at the end of treatment (day 90), the rates of clearing were 9/44 for diclofenac and 9/46 for vehicle (both 20%).
3. The above data using ITT analysis do not include all patients randomized (56 per group). They should be reanalyzed with inclusion of all randomized subjects. This has been done by the Biometrics Reviewer. The conclusions on this study are not affected by the reanalysis (diclofenac not superior over vehicle in primary variable, CLNS=0; p=0.08).

Secondary Efficacy Variables

Lesion Counts

			Delta Baseline			
		Baseline (mean)	Day 30 (mean)	Day 60 (mean)	Day 90 (mean)	30-d FU (mean)
CLNS	Diclofenac	9.2	-1.2	-2.8	-5.1	-6.6
	Vehicle	8.0	-1.5	-2.9	-3.9	-4.5
	p-value		0.542	0.907	0.138	0.006
TLNS	Diclofenac	9.2	-1.5	-3.3	-5.6	-6.8
	Vehicle	8.0	-1.8	-3.3	-4.1	-4.8
	p-value		0.524	0.928	0.060	0.006

*CLNS=cumulative lesion number score, TLNS=target lesion number score

Relatively few patients developed new lesions, and the lesions developed were also small in number. Thus, at the 30-day follow-up visit, there was the following mean numbers of new lesions: diclofenac - scalp 0.6 and hand 0.2 lesions; vehicle - scalp 0.5, forehead 0.3, central face 0.4, hand 0.4 and arm 0.5 lesions.