CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-184

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-184 **SUBMISSION DATE:** 9/30/99

PRODUCT: Tazorac® (tazarotene topical cream) 0.05%, 0.1%

SPONSOR: Allergan, Inc., Irvine, CA 92623

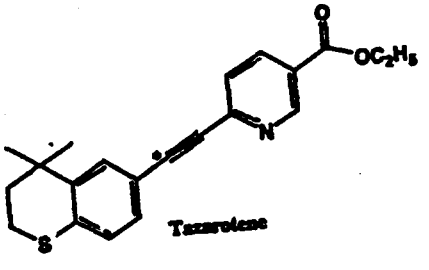
JUL 3 2000

REVIEWER: Tapash K. Ghosh, Ph.D.

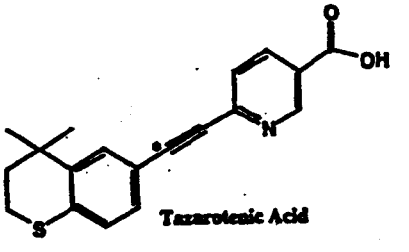
Review of a NDA

I. BACKGROUND

Tazarotene is a member of the acetylenic retinoids. It is intended for topical treatment of psoriasis. [redacted] Tazarotene represents the first topical retinoid useful for the treatment of psoriasis. It is converted to its active form, tazarotenic acid, in biological systems by deesterification. The exact mechanism of action of this compound is unknown. Clinical pharmacology studies suggest that tazarotene may correct three of the major pathogenic factors in psoriasis: keratinocyte hyperprolifearation, abnormal keratinocyte differentiation and infiltration of inflammatory components.



Tazarotene



Tazarotenic Acid

Tazarotene 0.05% and 0.1% gels indicated for the topical treatment of stable plaque psoriasis and Tazarotene 0.05% gel indicated for the topical treatment of acne vulgaris were approved under NDA 20-600 in June, 1997. To date, Tazorac® (topical tazarotene) creams 0.05%, 0.1% have not been marketed in any country. Tazorac® gels 0.05%, 0.1% (NDA 20-600) have been marketed in the United States, Canada, Latin America and the European Union. To date no tazarotene-containing formulations has been withdrawn from marketing in any country.

What is the purpose of this NDA?

In this application (NDA 21-184), the sponsor seeks approval of two concentrations (0.05% and 0.1%) of a tazarotene cream formulation for the treatment of plaque psoriasis. A cream formulation of tazarotene was desired to provide a moisturizing and emollient vehicle for tazarotene with reduced irritation relative to the approved gel. It was reportedly developed to offer greater flexibility to physicians and better acceptability and compliance to patients.

II. RECOMMENDATION

Topical dosing of tazarotene resulted in mostly nondetectable plasma concentration of the parent compound. Tazarotene is rapidly metabolized in the systemic circulation to its primary active metabolite, tazarotenic acid.

From well-controlled pharmacokinetic studies where psoriatic patients were given tazarotene cream 0.1% under clinical and exaggerated dosing conditions, the systemic exposure was low, with a bioavailability of 2-3% of the topical dose. Therapeutic drug monitoring of two pivotal efficacy studies conform that chronic topical application of the tazarotene cream leads to limited systemic exposure.

All these findings are comparable to findings obtained previously during submission of Tazorac® (tazarotene topical gel) 0.05%, 0.1% approved in June, 1997 and proven to be safe and effective topical treatment of retinoid responsive dermatoses.

Based on this review, NDA 21-184 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. A review of the PK data in this submission has resulted in certain changes in the appropriate sections of the product label. The suggested changes are included in the section "Labelling Comments" and have been conveyed to the reviewing division.

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III. CLINICAL PHARMACOLOGY

Tazarotene is a retinoid prodrug which is converted to its active form, tazarotenic acid, by rapid deesterification upon reaching the systemic circulation. The metabolic pathways of tazarotene include hydrolysis to form the free acid and oxidation to form sulfoxide and sulfone metabolites. The primary metabolites of tazarotene consists of the free acid (tazarotenic acid, active metabolite) in plasma, and the sulfoxide and tazarotenic acid in urine. In fecal excretion, polar metabolites (59%) (one of which was identified as an oxygenated derivative of tazarotenic acid) were found in addition to the above two metabolites (Figure 1). In studies using radiolabeled drug, both urinary and fecal excretion pathways were found to be equally important. Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid. Little parent compound could be detected in the plasma. Tazarotenic acid is highly bound to plasma proteins (>99%).

The mechanism of tazarotene in psoriasis is not defined. Topical tazarotene blocks induction of mouse epidermal ornithine decarboxylase (ODC) activity, which is associated with cell proliferation and hyperplasia. In cell culture and in vitro models of skin, tazarotene suppresses expression of MRP8, a marker of inflammation present in the epidermis of psoriasis subjects at high levels. In human keratinocyte cultures, it inhibits cornified envelope formation, whose build-up is an element of the psoriatic scale. The clinical significance of these findings is unknown.

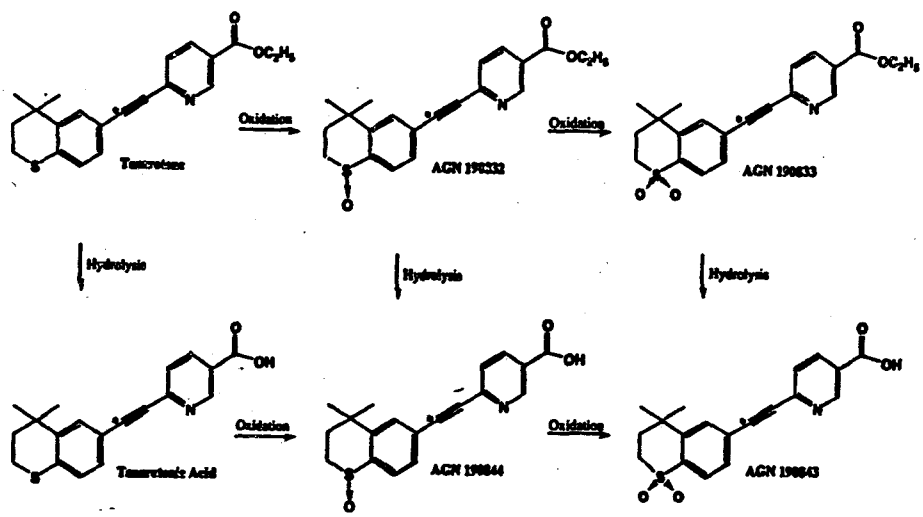

Figure 1: Metabolic pathway of Tazarotene

IV. PREVIOUS EXPERIENCE WITH TAZAROTENE GEL

An *in vitro* percutaneous absorption study, using radiolabeled drug and freshly excised human skin or human cadaver skin, indicated that approximately 4 to 5% of the applied dose from the gel was in the stratum corneum and 2 to 4% was in the viable epidermis-dermis layer 24 hours after topical application of the gel. Drug penetration across the skin and into the receptor fluid was less than 1% of the dose over 24 hours under the study conditions. A summary of the pivotal In Vivo studies with Tazorac Gel is presented below:

Table I: Summary of the Pivotal Studies with Tazorac Gel

Study #	Study Design	Tazarotene Cmax (ng/mL)	Active Metabolite (Tazaotenic Acid)			
			Cmax (ng/mL)	AUC (ng.h/mL)	Tmax (h)	$T_{1/2}$ (h)
R168-152-8606 (Multiple dose)	Healthy, n= 24 1st dose 0.1% gel, 6.8 g, over 20% BSA 12 hr exposure, unocluded	< LOQ	0.36±0.19	15.8±8.4	14	28.5±13.6
	Last dose	< LOQ	0.72±0.58	10.1±7.2	9	17.6±6.7
R168-153-8606 (Multiple dose)	Psoriatic Patients, n=5 1st dose Psoriatic skin:8-18% 5.23±2.05 g over affected area	0.016±0.013	1.04±0.94	22.2±19.1	10.2±2.7	18.3±3.8
	12 hr exposure, unoccluded Last dose	0.185±0.084	12.0±7.6	105.0±55.0	6.0±2.1	17.1±3.5
R168-154-8606 (Percutaneous absorption	Psoriatic Patients, n=6 0.1% gel, single dose, 2.28±0.19g over 5% BSA, 10 hr exposure, unoccluded , radiolabeled	Stratum corneum: 4.54±3.67% dose Epidermis: 1:38±1.28% dose Dermis: 0.97±0.89% dose Urine: 0.329±0.228% dose Fecal:0.426±0.472% dose				

V. FORMULATION

How does Tazorac® Cream differ from Tazorac® Gel?

Tazorac® Cream is an [redacted] whereas Tazorac® gel is a [redacted] gel formulation. The following table describes the line by line comparison of cream and gel formulations:

Ingredients	% w/w			
	0.1% Cream (#9087X)	0.05% Cream (#9103X)	0.1% Gel (#8606X)	0.05% Gel (#8607X-A)
Tazarotene	0.10	0.05	0.10	0.05
Benzyl Alcohol	1.0	1.0	1.0	1.0
Sodium Thiosulfate, $5H_2O$ USP	[redacted]		-	-
[redacted]				
Mineral Oil USP	[redacted]		-	-
Medium Chain Triglycerides			-	-
Carbomer 1342 NF			-	-
Sorbital Monooleate NF			-	-
[redacted]				
Carbomer 934P	[redacted]			
[redacted]				
Purified Water	[redacted]			

VI. ANALYTICAL

[redacted]

A highly sensitive and selective [redacted] method was validated to determine both Tazarotene (AGN 190168) and Tazarotenic Acid (AGN 190299) concentrations in human plasma. The method was found to be reliable, precise and accurate for quantitative measurement of concentrations of both species in human plasma between [redacted] for [redacted] samples. Method validation data were submitted and are considered satisfactory. Summary of the method validation is presented below:

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Due to improved sensitivity of new instrumentation, the assay was re-qualified at lower detection limits for the following studies:

Study /Report Number	Type of Biological Matrix	Method	Sensitivity of Method (Range)	Analysis
190168-016C (PK-99-060)	Plasma			Tazarotene Tazarotenic Acid
190168-017C (PK-99-044)	Plasma			Tazarotene Tazarotenic Acid
190168-023C (PK-99-085)	Plasma			Tazarotene Tazarotenic Acid

The method employed D7-tazarotene and D7-tazarotenic acid as internal standards and used — plasma sample volume. The automated extraction system preconditioned the

VII. SUMMARY OF SUPPORTIVE IN-VIVO STUDIES FOR TAZORAC CREAM

Are the studies done in support of this NDA acceptable?

The sponsor listed the following studies to provide ***in vitro*** and ***in vivo*** pharmacokinetics data in support of proposed tazarotene creams. Summary of each of these studies are described in the following section:

- **Study I.** The Screening of Tazarotene Cream Formulations by Determining the In-Vitro Skin Permeation of Tazarotene Through Human Cadaver Skin (PK-96-003) (Study Period: June 1995 – April 1996)
- **Study II.** Multicenter, Double-Blind, Randomized, Vehicle-Controlled Study of the Safety and Efficacy 0f 0.05% and 0.1% Tazarotene Creams Applied Once Daily for 12 Weeks in the Treatment of Plaque Psoriasis (PK-99-044) (Study Period: 12/30/97 – 10/16/98)
- **Study III.** Multicenter, Double-Blind, Randomized, Vehicle-Controlled Study of the Safety and Efficacy 0f 0.05% and 0.1% Tazarotene Creams Applied Once Daily for 12 Weeks, With a 12-Week Follow-Up, in the Treatment of Plaque Psoriasis (PK-99-060) (Study Period: 12/29/97 – 01/22/99)
- **Study IV.** Skin Distribution of 0.1% (w/w) ^{14}C-Tazarotene Cream in the Hanford Minipig after Daily Topical Application to the Skin for 1, 5, and 7 Days (PK-99-046)(Study Period: June 1998 – July 1998)
- **Study V.** An Open-label, Multi-Center, Pharmacokinetics Study of Tazarotene 0.1% Cream Applied Once Daily for 14 Days in the Treatment of Plaque Psoriasis (Study # 190168-023C; Document # PK-099-085; Study Period: Jan 1999 – May 1999)
- **Study VI.** An Open-label, Single-Center, Pharmacokinetics Study of Tazarotene 0.1% Cream Applied Once Daily for 14 Days in the Treatment of Plaque Psoriasis (Study # 190168-024C) (Study Period: August 7 – October 13, 1998) (Bioanalytical site and period November 2 – 15, 1999; Report Signed 1-21-00).

Study I. The Screening of Tazarotene Cream Formulations by Determining the In-Vitro Skin Permeation of Tazarotene Through Human Cadaver Skin (PK-96-003)(Study Period: June 1995 – April 1996)

To evaluate tazarotene cream formulations for further product development, the *in vitro* penetration of tazarotene from prototype cream formulations (Table II) through human cadaver skin was determined.

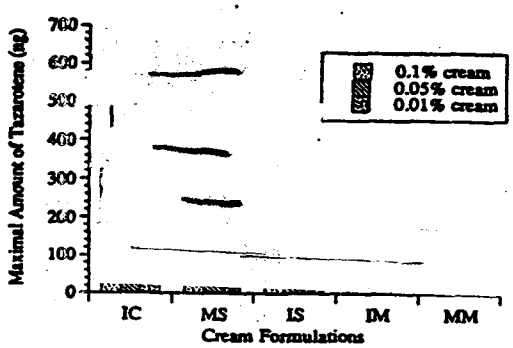

Figure 2: The maximal amount of tazarotene that penetrates human cadaver skin over a 28 hour period *in - vitro* (Data are the mean ± SD for 6 replicates)

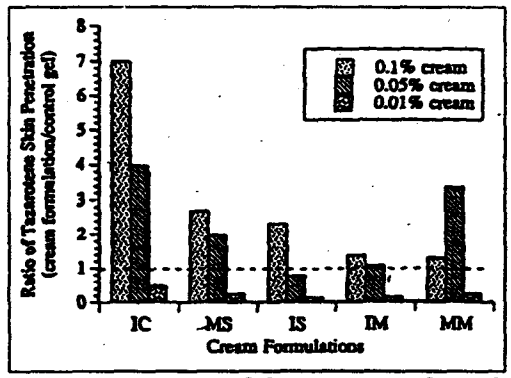

Figure 3: Ratios of tazarotene skin permeation data of the test cream formulations to control gel. The dotted Line represents a ratio of 1, where cream formulation penetration data are equivalent to the control Gel.

Table II: Maximal Amounts of Tazarotene Penetrated from Prototype Cream Formulations Through Human Cadaver Skin

Experimental Run	Tazarotene Strength	Formulation Identification	Maximal Tazarotene Amount (ng) Mean	SD	Ratio to the Control
#1	0.1%		13.5	6.7	0.127
	0.1%		129	53	1.210
	0.1%		107	58	1
#2	0.1%		221	106	0.854
	0.1%		78.9	42.8	0.306
	0.1%	2	298	196	1.15
	0.1%		258	164	1
#3	0.1%		948	715	3.26
	0.1%		1230	1050	4.22
	0.1%		290	477	1
#4	0.1%		443	235	0.884
	0.1%		501	513	1
#5	0.1%		308	89	0.615
	0.1%		538	545	1
#6	0.1%		248	119	0.810
	0.1%		306	450	1
#7	0.1%		235	144	0.773
	0.1%		304	573	1
#8	0.05%		117	67	5.32
	0.05%		66.5	59.4	2.86
	0.05%		250	167	10.8
	0.05%		77.7	42.3	3.34
	0.05%		47.5	15.1	2.04
	0.05%		23.3	14.6	1
#9	0.05%		60.3	53.9	1.02
	0.05%		20.0	14.4	0.340
	0.05%		31.4	15.9	0.532
	0.05%		58.9	58.3	1
#10	0.1%		72.8	56.1	0.992
	0.1%		69.9	36.9	0.952
	0.1%		73.4	58.2	1

Experimental Run	Tazarotene Strength	Formulation Identification	Maximal Tazarotene Amount (ng) Mean	SD	Ratio to the Control
#11	0.1%		67.9	59.9	1.39
	0.1%		341	286	6.99
	0.1%		63.0	51.1	1.29
	0.1%		113	88	2.33
	0.1%		131	142	2.69
	0.1%		121	103	2.47
	0.1%		48.7	71.6	1
#12	0.05%		179	84	5.16
	0.05%		357	204	10.3
	0.05%		165	102	4.78
	0.05%		151	128	4.38
	0.05%		177	76	5.68
	0.05%		34.6	40.4	1
#13	0.1%		332	212	5.33
	0.1%		280	181	4.48
	0.1%		179	122	2.87
	0.01%		14.9	12.1	0.239
	0.01%		15.8	17.0	0.253
	0.1%		62.4	93.7	1

Experimental Run	Tazarotene Strength	Formulation Identification	Maximal Tazarotene Amount (ng) Mean	SD	Ratio to the Control
#14	0.01%		15.9	23.1	0.167
	0.01%		14.7	12.2	0.154
	0.01%		21.3	19.0	0.224
	0.01%		46.8	50.3	0.492
	0.01%		8.25	4.59	0.087
	0.05%		51.4	57.7	3.36
	0.1%		95.1	153	1
#15	0.05%		26.5	10.7	1.16
	0.05%		45.2	38.9	1.98
	0.05%		25.1	19.0	1.10
	0.05%		18.1	15.4	0.794
	0.05%		90.7	36.9	3.98
	0.05%		55.6	19.2	2.44
	0.05%		22.8	27.4	1.00
	0.1%		49.3	66.5	1.00

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MIG = miglyol oil
DM = dimethicone
IC = IPM and CYC
IS = IPM and SQ
MM = MIG and MO

SQ = squalane
IPM = isopropyl myristate
ID = IPM and DM
IM = IPM and MO

MO = mineral oil
CYC = cyclomethicone
MC = MIG and CYC
MS = MIG and SQ

Table III: Summary of Penetration Characteristics for Prospective Formulations

Formulation Identification	Tazarotene Strength	Formulation No.	Maximal Tazarotene Amount (ng) Mean	SD	Ratio to Control
[redacted]	0.1%	8887X	341	286	6.99
	0.05%	8886X	90.7	36.9	3.98
	0.01%	8885X	46.8	50.3	0.492
	0.1%	8878X	131	142	2.69
	0.05%	8877X	45.2	38.9	1.98
	0.01%	8876X	15.8	17.0	0.253
	0.1%	8884X	113	88	2.33
	0.05%	8883X	18.1	15.4	0.794
	0.01%	8882X	14.7	12.2	0.154
	0.1%	8890X	67.9	59.9	1.39
	0.05%	8889X	25.1	19.0	1.10
	0.01%	8888X	15.9	23.1	0.167
	0.1%	8881X	63.0	51.1	1.29
	0.05%	8880X	51.4	57.7	3.36
	0.01%	8879X	14.9	12.1	0.239

MIG = miglyol oil
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Table IV: Manufacturing References for the Formulations Selected for Clinical Testing

Formulation Identification	X Number	Manufacture Reference	Release Assay (% w/w)	Assay Reference
	8887X	R-1994-3276-104		R-1994-3387-112
	8886X	R-1994-3387-127		R-1994-3387-132
	8885X	R-1995-3531-158		R-1994-3387-133
	8878X	R-1994-3387-105		R-1994-3387-112
	8877X	R-1995-3531-155		R-1994-3387-132
	8876X	R-1995-3531-145		R-1994-3387-133
	8884X	R-1994-3276-102		R-1994-3387-112
	8883X	R-1995-3531-157		R-1994-3387-132
	8882X	R-1995-3531-149		R-1994-3387-133
	8890X	R-1994-3276-103		R-1994-3387-112
	8889X	R-1995-3531-158		R-1994-3387-132
	8888X	R-1995-3531-148		R-1994-3387-133
	8881X	R-1994-3276-101		R-1994-3387-112
	8880X	R-1995-3531-156		R-1994-3387-132
	8879X	R-1995-3531-146		R-1994-3387-133

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Five prospective formulations (Table III) were selected based upon their penetration, pharmacological (rhino mouse efficacy model), and toxicological (rat skin irritancy model) characteristics. Figures 2 and 3 contain the tazarotene skin penetration data for the 5 selected creams, at 3 strengths, that was tested in the primary skin irritancy study in humans. The range for the maximal amount of tazarotene penetration from these 0.1%, 0.05% and 0.01% creams was _____ respectively. Table IV describes manufacture references for the formulations selected for clinical testing.

Among these cream formulations, the "IC" formulation showed the greatest degree of penetration at each cream strength. Similarly, the "IC" formulations gave the highest ratio to control values at their respective tazarotene strength. In conclusion, these selected cream formulations demonstrated that tazarotene was released from the cream bases and the amount of tazarotene that passed through human cadaver skin was equal to or greater than that for the tazarotene gel formulation. One tazarotene cream formulation type containing miglyol oil and mineral oil (Formulation Nos. – 8881X, 8880X and 8879X) was selected for further development.

Comments:

- In absence of pharmacological and toxicological data, the rationale behind selection of five prospective formulations (Table III) is not very clear. Variability in the control data (Mean ± SD) precludes ignoring any set of data from the results obtained. Also, formulation Nos. – 8881X, 8880X and 8879X do not match formulations 9087X and 9103X used in human PK studies. The selection process of this final to be marketed formulation is not presented anywhere in this section.

- It was also reported in Table II of the same report that experimental runs 1-7 were performed on 15 mm diameter Franz cells whereas the remainder of experiments were tested on the 9 mm diameter size cells. It's interesting to note that the orifice diameter should have been taken into consideration in standardizing the penetration amounts from different formulations. It is known that amount permeated in a static diffusion cell is directly proportional to the orifice size. Therefore, penetration rate should have been calculated in the unit of ng/cm^2 to resolve the effect of orifice diameter.

- It has been mentioned in the "Data Analysis" of the report that "For each formulation, 6 diffusion cells were initially set up. If the skin barrier function was compromised, as detected by abnormally high drug permeability or back-diffusion of reservoir fluid to the top of the mounted skin sample, then the sample was rejected". Therefore, it appears that in Table II and III, Maximal Tazarotene Amount (ng) (Mean ± SD) reported has different numbers of replicates for different runs. Therefore, number of replicates (n) for each formulation for each run should have been mentioned for a more meaningful evaluation.

- Formulation Identification (Table II) for experimental runs up to # 8 is understandable. The terms "Gramicotril" and "Naftifine" used in runs # 9 and 10 are not clear. Similarly all the terms used in runs # 11 onwards remain unclear in terms of their compositions.

Study II. Multicenter, Double-Blind, Randomized, Vehicle-Controlled Study of the Safety and Efficacy 0f 0.05% and 0.1% Tazarotene Creams Applied Once Daily for 12 Weeks in the Treatment of Plaque Psoriasis (PK-99-044) (12/30/97 – 10/16/98)

This report summarizes the therapeutic drug monitoring (TDM) results, which was conducted at 5 of 17 clinical sites. Male and female patients, 18 years of age or older, with psoriatic plaques were dosed once daily for up to 12 weeks with tazarotene 0.05% or 0.1% or vehicle cream (Formulation numbers 9103X, 9087X, 9104X respectively). Tazarotene 0.05% or 0.1% or vehicle cream was applied once daily in the evening to affected areas by the patients. For TDM sampling days, doses were applied in the morning. Blood samples from the patients were collected at weeks 4 and 8, before and 3-10 hours postdose, for determination of plasma concentrations of tazarotene (the parent

drug) and tazarotenic acid (the active metabolite). The plasma samples were analyzed using a validated ——————————————— The lower limit of quantitation was validated at ——— for both tazarotene and tazarotenic acid.

For computational purposes, below limits of quantitation ——— of plasma tazarotenic acid concentrations were replaced with "zero" value. Paired t-test analysis was performed to determine if there were any changes between week 4 and week 8 within each of the treatment groups ——. The difference from the pre- and postdose plasma tazarotenic acid concentrations were calculated and the Wilcoxon sign-rank analysis was performed to determine any differences between pre- and postdose concentrations within each of the treatment groups.

From a total of 37 patients who received tazarotene cream 0.05% treatment for up to 12 weeks and had their plasma assayed, no tazarotene was detected in any of their samples, that is, all plasma tazarotene concentrations were below the lower limit of quantitation (< ——— However, plasma tazarotenic acid concentrations were detected in 19 of 37 (51%) patients with no concentration greater than ——— Of 32 patients treated topically with tazarotene cream 0.1%, only 2 (6%) patients had detectable tazarotene plasma concentrations. However 23 of 32 (72%) patients had detectable plasma tazarotenic acid concentrations , the highest at ——— . No patients (n=36) in the vehicle cream treatment group had detectable plasma tazarotene or tazarotenic acid concentrations. Table V summarizes the descriptive statistics for the plasma tazarotenic acid concentrations.

Table V: Summary of Dosing Information and Plasma Tazarotenic Acid Concentrations (ng/mL) during 4 and 8 Weeks of Treatment with Tazarotene Cream (0.05% or 0.1%) for Plaque Psoriasis

	Tazarotene 0.05% Cream Treatment									
	Week 4					Week 8				
	Dose Wt (g)	% BSA	C_{Pre} (ng/mL)	C_{Post} (ng/mL)	Time (hr)	Dose Wt (g)	% BSA	C_{Pre} (ng/mL)	C_{Post} (ng/mL)	Time (hr)
Mean	2.26	10	0.0283	0.0401	4.38	2.08	10	0.0266	0.0427	4.48
Median	1.11	6	0	0	4.21	1.62	6	0	0	4.00
S.D.	2.93	12	0.0486	0.0591	1.24	2.18	12	0.0498	0.0709	1.59
Max	13.6	70	———		7.67	11.3	70	———		9.00
Min	0.19	2	———		3.00	0.3	2	———		3.00
N	38	38	36	36	36	31	37	28	28	28
	Tazarotene 0.1% Cream Treatment									
Mean	2.13	11	0.0716	0.155	3.92	2.43	11	0.0471	0.111	3.97
Median	1.52	8	0.0530	0.103	3.46	1.23	7	0	0.0684	3.75
S.D.	2.07	10	0.0944	0.205	1.05	3.15	10	0.0627	0.155	1.13
Max	8.86	40	———		7.00	16.4	36	———		7.00
Min	0.10	1	———		2.75	0.340	1.5	———		2.08
N	32	33	32	32	32	28	30	27	27	27

Paired t-test analysis for dose weight, percent of psoriasis involvement (% BSA) and the time of blood collection after dosing showed no significant difference of these parameters between the week 4 and week 8. However, comparison of the pre- and postdose plasma tazarotenic acid concentrations for each cream formulations (0.05% and 0.1%) indicates that postdose concentrations were statistically significantly higher than predose concentrations both at 4 and 8 weeks respectively. Moreover, the difference between pre- and postdose concentrations is found to be much greater with tazarotene 0.1% cream compared to 0.05% cream.

Study III. Multicenter, Double-Blind, Randomized, Vehicle-Controlled Study of the Safety and Efficacy 0f 0.05% and 0.1% Tazarotene Creams Applied Once Daily for 12 Weeks, With a 12-Week Follow-Up, in the Treatment of Plaque Psoriasis (PK-99-060) (12/29/97 – 01/22/99)

An identical protocol as described in the above study (PK-99-044) was followed for this study. From a total of 32 patients who received tazarotene cream 0.05% treatment for up to 12 weeks and had their plasma assayed, no tazarotene was detected in any of their samples, that is, all plasma tazarotene concentrations were below the lower limit of quantitation [redacted] However, plasma tazarotenic acid concentrations were detected in 12 of 32 (38%) patients with no concentration greater than [redacted] Of 38 patients treated topically with tazarotene cream 0.1%, only 1 patient had detectable tazarotene plasma concentration. However 24 of 38 patients had detectable plasma tazarotenic acid concentrations , the highest at [redacted] One (1) patient (n=41) in the vehicle cream treatment group had detectable plasma tazarotene concentration (considered spurious) and no patient had detectable tazarotenic acid concentration.Table VI summarizes the descriptive statistics for the plasma tazarotenic acid concentrations.

Table VI: Summary of Dosing Information and Plasma Tazarotenic Acid Concentrations (ng/mL) during 4 and 8 Weeks of Treatment with Tazarotene Cream (0.05% or 0.1%) for Plaque Psoriasis

	Tazarotene 0.05% Cream Treatment									
	Week 4					Week 8				
	Dose Wt (g)	% BSA	C_{Pre} (ng/mL)	C_{Post} (ng/mL)	Time (hr)	Dose Wt (g)	% BSA	C_{Pre} (ng/mL)	C_{Post} (ng/mL)	Time (hr)
Mean	4.74	12	0.0296	0.0825	4.05	4.45	8	0.0639	0.130	5.18
Median	2.21	4	0	0	3.83	4.46	3	0	0	5.00
S.D.	5.86	20	0.0756	0.163	1.05	2.99	10	0.104	0.169	1.47
Max	27.6	90	[redacted]		6.58	9.05	37	[redacted]		7.45
Min	0.32	2	[redacted]		2.83	0.480	2	[redacted]		3.17
N	31	31	30	31	31	15	15	15	15	15
	Tazarotene 0.1% Cream Treatment									
Mean	3.77	7	0.185	0.311	4.86	3.80	7	0.157	0.348	4.58
Median	2.52	5	0	0.122	4.25	2.53	5	0	0.0952	4.08
S.D.	3.10	6	0.398	0.546	1.96	3.84	7	0.34	0.518	1.87
Max	11.3	28	[redacted]		9.83	15.3	28	[redacted]		9.68
Min	0.21	0.1	[redacted]		3.00	0.33	0.1	[redacted]		2.25
N	36	36	36	36	35	29	29	30	30	29

Paired t-test analysis for dose weight, percent of psoriasis involvement (% BSA) and the time of blood collection after dosing showed no significant difference of these parameters between the week 4 and week 8. However, comparison of the pre- and postdose plasma tazarotenic acid concentrations for each cream formulations (0.05% and 0.1%) indicates that postdose concentrations were statistically significantly higher than predose concentrations both at 4 and 8 weeks respectively. Moreover, the difference between pre- and postdose concentrations is found to be much greater with tazarotene 0.1% cream compared to 0.05% cream.

Comments:

- Though the objectives of both these studies (***PK-99-044, PK-99-060***) were to determine safety and efficacy of 0.05% and 0.1% creams on psoriatic patients, the data presented here is a subset of the population evaluated for therapeutic drug monitoring (TDM) purpose. Therefore, no information on efficacy outcome is available in the reports provided.

Table VII: Summary of Therapeutic Drug Monitoring Studies

Study #	PK 99-044				PK 99-060			
Strength	0.05%		0.1%		0.05%		0.1%	
Parameters	Wk 4	Wk 8	Wk 4	Wk 8	Wk 4	Wk 8	Wk 4	Wk 8
Dose ± SD	2.26 ±2.93	2.08 ±2.18	2.13 ±2.07	2.43 ± 3.15	4.74 ±5.86	4.45 ±2.99	3.77 ±3.10	3.80 ±3.84
%BSA ± SD	10 ± 12	10 ± 12	11 ± 10	11 ± 10	12 ± 20	8 ± 10	7 ± 6	7 ± 7
C_{Pre} ± SD	0.0283 ±0.0486	0.0266 ±0.0498	0.0716 ±0.0944	0.0471± 0.0627	0.0296 ±0.0756	0.0639± 0.0104	0.185± 0.398	0.157 ±0.34
C_{Post} ± SD	0.0401 ±0.0591	0.0427 ±0.0709	0.155 ±0.205	0.111 ±0.155	0.0825 ±0.163	0.130 ±0.169	0.311 ±0.546	0.348 ±0.518

- It is evident from the above summary table VII of the two TDM studies that there is a clear difference between the dose applied at both time points (Wk 4 and Wk 8) between the two studies (PK 99-044 and PK 99-060) and that has reflected in the pre- and post dose applied concentrations. It has been found that post dose concentration is at least double in the second study (PK 99-060) where applied dose was also 2 times higher than the first study. Therefore, there is a clear relationship between amount of dose applied and the plasma concentration whereas relationship between % BSA and plasma concentration is not that evident. The sponsor did not address these findings in their discussion.

Study IV. Skin Distribution of 0.1% (w/w) ^{14}C-Tazarotene Cream in the Hanford Minipig after Daily Topical Application to the Skin for 1, 5, and 7 Days (PK-99-046)(Study Period: June 1998 – July 1998)

Skin distribution of ^{14}C-Tazarotene after single and multiple topical administration of a 0.1% (w/w) tazarotene cream was studied in three male minipigs, weighing between 11 – 15 kg. Seven different dosing sites of 5 cm^2 on the dorsal area of each minipig were protected with a teflon tape covered ring to prevent the cross contamination of the dosing sites. The test formulation (35.7 µg of tazarotene, 2.0 µCi in 55 µL of cream) was applied daily for 1, 5, and 7 days and each daily dose was removed at 24 hours post-dose. Other application sites were dosed for 7 days and then allowed to washout for up to 4 weeks after the removal of the last dose. At the time of euthanasia, the minipig was immobilized in a sling and euthanized with intracardiac injection of [redacted] Unabsorbed drug from the dosed sites were removed by cotton-tipped swabs soaked in water (5 swab/site). For all dosing sites, ten tape strips were taken, weighed and saved for analysis. Dosing sites were then excised from the animal. Subcutaneous fat and fascia were cut away. Excised skin samples were microwaved (@ high power – 1 min) in order to separate skin layers. The epidermis was carefully scraped away from the dermis with a scalpel. Animals were euthanized, the skin of each dosing site was excised, and skin tissues (stratum corneum, epidermis and dermis) were collected. Radioactivity in each sample was determined by [redacted]. The concentration in all dermal tissues (stratum corneum, epidermis, and dermis) versus time were plotted on logarithmic scale. Pharmacokinetic analysis was performed using Excel®. Recoveries of ^{14}C-Tazarotene 24 hours after a Single Topical Administration of a 0.1% Cream to the Skin of Male Minipigs is presented in Table VIII whereas Half-life and Concentrations of ^{14}C-Tazarotene in Skin Tissues after Topical Daily Administration of a 0.1% Cream to the Skin of Male Minipigs for up to 7 Days is presented in Table IX below. The absorption and elimination profile of ^{14}C-Tazarotene form different layers of minipig skin following multiple applications up to 7 days is described in Figure 4.

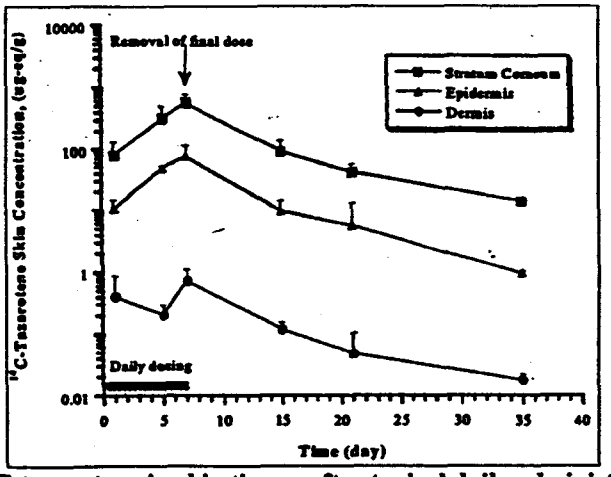

Figure 4: Concentrations of ^{14}C-tazarotene in skin tissues after topical daily administration of a 0.1% cream to the skin of male minipigs for up to 7 days (Mean±SD of 3 values)

Table VIII: Recoveries of ^{14}C-Tazarotene 24 hours after a Single Topical Administration of a 0.1% Cream to the Skin of Male Minipigs

Sample	Percent of Dose	Radioactive Concentration(μg-eq/g)
Stratum Corneum	11.8 ± 7.9	80.6 ± 51.70
Epidermis	4.69 ± 1.89	10.5 ± 4.5
Dermis	4.58 ± 4.74	0.412 ± 0.460
Unabsorbed (swabs)	48.2 ± 4.10	?
Teflon® tape	13.6 ± 7.90	?
Total	82.8 ± 5.0	?

Table IX: Half-life and Concentrations of ^{14}C-Tazarotene in Skin Tissues after Topical Daily Administration of a 0.1% Cream to the Skin of Male Minipigs for up to 7 Days

Sample	Radioactive Concentration(μg-eq/g)						$T_{1/2}$ (Days)
	Day1	Day5	Day7	Day (-7)	Day (-14)	Day (-28)	
Stratum Corneum	80.6 ± 51.70	316±177	573±200	94.3±46.9	42.1±13.8	13.7±1.9	5.41
Epidermis	10.5 ± 4.5	48.3±4.22	76.8±38.7	9.63±4.64	5.54±7.27	0.96±0.04	4.65
Dermis	0.412 ± 0.460	0.206±0.086	0.732±0.370	0.12±0.04	0.047±0.055	0.017±0.004	5.39

It is evident that following topical administration of a 0.1% cream formulation to male minipigs, tazarotene distributed substantially in different layers of skin. Drug accumulation of ^{14}C-Tazarotene in each skin layer was observed. Drug concentrations following 7 daily doses were at least doubled than those after the first dose. After 5 and 7 days of dosing, a concentration gradient was seen in the skin layers, with 100-fold decline in concentrations going from the outermost layer (stratum corneum) to the deeper skin tissues (epidermis → dermis). Upon multiple topical daily application, an apparent ^{14}C-Tazarotene half-life was approximately 5 days.

Comments:

- The sponsor could not account for the rest 17.2% (100 - 82.8) of applied dose (single dose, Table VIII) and explained it as "drug loss". However they did not make any attempt to measure blood level of ^{14}C-Tazarotene which could have accounted for the mass balance. Moreover, it also could give data on systemic exposure and bioavailability of Tazarotene in minipigs.

- The sponsor did not provide any explanation for the disposition of Tazarotene from different layers of skin. Theoretically, drug from the uppermost stratum corneum should travel through epidermis and dermis to reach systemic circulation for eventual elimination. In that circumstances, due to accumulation factor, half-life of the drug in different layers should be in the following order: Dermis > Epidermis > Stratum corneum. However, Figure 4 showed surprisingly parallel elimination.

Study V. An Open-label, Multi-Center, Pharmacokinetics Study of Tazarotene 0.1% Cream Applied Once Daily for 14 Days in the Treatment of Plaque Psoriasis (Study # 190168-023C; Document # PK-099-085)

The objective of the study was to determine safety and pharmacokinetics of two topical application rates, clinical and exaggerated use conditions, of tazarotene cream 0.1% (9087X) once-daily treatment for 14 days in plaque psoriasis.

This was an open-label, multi-center, stratified, parallel-group clinical pharmacokinetic study in plaque psoriasis patients (n = 11) to assess the safety of two topical application rates (2 mg/cm^2 and 10 mg/cm^2) of tazarotene cream 0.1% after controlled clinical and exaggerated conditions. Patients received a single topical application followed by 13 additional daily applications for total of 14 doses. Based on the dosing calculations, the quantity of study medication for each patient was weighed out in an appropriate weight container prior to dosing. The site personnel applied the study medication to the psoriatic lesions every evening throughout the study. All psoriatic plaques excluding the scalp and intertiginous areas were treated.

Group assignment was based on the percent body surface area of involvement determined at baseline (Day 0). The following scheme was used for patient assignment:

	Percent Psoriatic Involvement (% PI)* at Baseline (Day 0)	Dosage Group Assigned
1st patient with	% PI ≥ 5%	10 mg/cm^2
2nd patient with	% PI ≥ 5%	2 mg/cm^2
3rd patient with	% PI ≥ 5%	10 mg/cm^2
4th patient with	% PI ≥ 5%	2 mg/cm^2
	% PI ≥ 10%	10 mg/cm^2
1st patient with	% PI ≥ 10%	2 mg/cm^2
2nd patient with	% PI ≥ 10%	10 mg/cm^2
3rd patient with	% PI ≥ 10%	2 mg/cm^2
4th patient with		
	% PI ≥ 15%	10 mg/cm^2
1st patient with	% PI ≥ 15%	2 mg/cm^2
2nd patient with		

An aliquot of 10 mL blood was collected in EDTA-treated tubes from the superficial vein in the forearm of each patient as schedule. Immediately after collection, the blood was centrifuged at 4^0 C at approximately ——— minutes to separate the plasma from the blood cells. The plasma samples were stored frozen below -15^0 C and then shipped on dry-ice to Allergan (Irvine, CA).

The plasma samples were assayed for tazarotene and tazarotenic acid using a validated ———— Briefly, the assay using 1 ml of plasma, had a calibration curve from ———— . Sample preparation used automated solid phase extraction on C-18 cartridges. The method employed positive ion multiple reaction monitoring modes using deuterated internal standards.

For each completed patient, the following pharmacokinetic parameters were calculated whenever possible, from the serial plasma tazarotenic acid concentrations after the single dose or multiple dose:

C_{max}, T_{max}, K_e, $t_{1/2}$, AUC_{0-t}, AUC_{∞}, AUC_{24} and F.

The bioavailability or percent of dose systemically available (F) of tazarotenic acid was calculated using:

$$F = \frac{AUC_{24,\,TOP}}{AUC_{\infty,\,IV}} * \frac{Dose_{IV,\,168}}{Dose_{TOP,\,168}}$$

Where, $AUC_{24,\,TOP}$ is the AUC_{24} of tazarotenic acid after topical dosing in the present study, $AUC_{\infty,\,IV}$ was the mean of AUC_{∞} of tazarotenic acid from 8 subjects after an intravenous dose of tazarotene, $Dose_{IV,\,168}$ was the mean total intravenous dose of tazarotene (in µg), and $Dose_{TOP,\,168}$ was the total topical daily dose of tazarotene (in µg) from the present study. The intravenous data were obtained from Allergan Study R168-155-8757 in which tazarotene was administered intravenously to healthy subjects as a dosage of 15 µg/kg over 20 minutes (PKDM Report PK-950049). All bioavailability calculations assume the dose was quantitatively metabolized from tazarotene to tazarotenic acid in both normal and psoriatic populations, and also assumed a constant clearance between dose and between studies. Bioavailability for Study Day 0 (after the first topical dose) used AUC_{∞} while F calculated for Study Days 8 and 15 used AUC_{24} values.

Table X: Summary of Body Surface Involvement and Dosage

Study Day	% Psoriatic Involvement	Targeted Dose Area (cm^2)	Actual Cream Dose Weight (g)	% of Targeted Dose	Tazarotene Dosage ($\mu g/cm^2$)
Application Rate = 2 mg/cm^2 (N=5)					
0	16±12	3260±2740	6.54±5.41	102±4	74.1±51.3
8	18±13	3540±2760	7.24±5.26	108±11	84.4±52.6
15	16±13	3290±2846	6.71±5.59	103±7	76.8±52.5
Mean	**17±12**	**3370±2580**	**6.83±5.03**	**104±8**	**78.4±48.5**
Application Rate = 10 mg/cm^2 (N=4)					
0	14±10	2560±1790	26.3±18.3	103±1	364±298
8	12±10	2200±1800	22.1±18.1	100±2	303±279
15	10±7	1800±1330	18.2±13.6	101±2	243±187
Mean	**12±9**	**2180±1530**	**22.2±15.6**	**101±2**	**303±240**

Table XI: Summary of the Pharmacokinetic Parameters of Tazarotenic Acid Following Topical Administration of Tazarotene Cream 0.1% Daily to Psoriatic Patients for 14 Days

Day	Parameters	Cmax (ng/mL)	Tmax (hr)	AUC_{24} (ng.hr/mL)	$t_{1/2}$ (hr)	F (% of dose)
Application Rate: 2 mg/cm^2						
0	Mean	0.400	11	23.6	13.6	1.07
	SD	0.381	2	NA	NA	NA
	Median	0.232	12	NA	NA	NA
	Max	0.836	12	NA	NA	NA
	Min	0.133	9	NA	NA	NA
	N	3	3	1	1	1
8	Mean	1.58	7	23.5	NA	1.96
	SD	1.54	2	21.9	NA	1.12
	Median	1.19	6	18.9	NA	2.06
	Max	4.01	9	56.6	NA	3.33
	Min	0.109	6	1.27	NA	0.358
	N	5	5	5	NA	5
15	Mean	2.31	8	31.2	15.4	2.54
	SD	2.78	3	35.2	NA	1.53
	Median	1.02	6	17.5	NA	2.50
	Max	6.85	12	88.3	NA	4.08
	Min	0.131	6	0.960	NA	0.4000
	N	5	5	5	1	5
Application Rate: 10 mg/cm^2						
0	Mean	0.549	11	45.6	19.2	0.630
	SD	0.475	3	NA	NA	NA
	Median	0.353	12	NA	NA	NA
	Max	1.250	12	NA	NA	NA
	Min	0.241	6	NA	NA	NA
	N	4	4	1	1	1
8	Mean	3.380	8	51.1	NA	1.45
	SD	4.170	3	60.9	NA	0.69
	Median	1.770	8	27.7	NA	1.41
	Max	9.550	12	141.0	NA	2.25
	Min	0.419	6	8.00	NA	0.743
	N	4	4	4	NA	4
15	Mean	3.070	7	46.4	31.3	1.83
	SD	2.630	2	37.6	7.4	0.47
	Median	2.570	6	37.1	25.7	1.93
	Max	6.400	9	97.1	65.0	2.27
	Min	0.746	6	14.0	24.1	1.21
	N	4	4	4	3	4

Table XII: Summary of Within and Between Group Comparisons of Pharmacokinetic Parameters

Parameter	Study Day	Within Group p-value: Application Rates 2 mg/cm²	N	10 mg/cm²	N	All Patients	N	Between Group p-value
Cmax	0 vs 0	NA	3	NA	4	NA	7	0.289
	0 vs 8	0.250	3	0.125	4	0.016	7	0.724
	0 vs 15	0.250	3	0.125	4	0.016	7	0.724
T max	0 vs 0	NA	3	NA	4	NA	7	1.00
	0 vs 8	0.250	3	0.500	4	0.063	7	0.350
	0 vs 15	0.250	3	0.250	4	0.031	7	1.00
AUC_{24}	0 vs 0	NA	3	NA	4	NA	7	0.289
	0 vs 8	0.250	3	0.125	4	0.016	7	0.724
	0 vs 15	0.250	3	0.125	4	0.016	7	1.00
$t_{1/2}$	0 vs 0	NA	3	NA	4	NA	7	NA
	0 vs 15	NA	3	NA	4	NA	7	NA

A total of 11 patients were enrolled, with 9 completed (Patients 001, 003, 004, 005, 006, 007, 008, 009, and 011) and 2 patients discontinued (Patients 002 and 010). Among the 9 patients completed, 7 were female and 2 were male. Patient age ranged from 23 to 68 years, and their body weight ranged from 59.5 to 104 Kg. All patients were caucasian.

Tazarotene plasma concentrations were generally nonquantifiable in most of the patients. Of 305 plasma samples collected, only 9 samples had quantifiable tazarotene concentrations, with the highest at ———— On the contrary, 242 samples had quantifiable tazarotenic acid concentrations demonstrating rapid hydrolysis of tazarotene to tazarotenic acid. Therefore, all the pharmacokinetic parameters were established based on tazarotenic acid concentration.

The mean plasma tazarotenic acid concentration-time profiles are graphically presented in Figures 5 and 6 for application rates of 2 and 10 mg/cm^2 respectively. Table XII lists the descriptive statistical summary of pharmacokinetic parameters for tazarotenic acid for Study Days 0, 8 and 15.

The data suggested that the bioavailability increased from 0.63% and 1.07% on Day 0 to 1.83% and 2.54% upon multiple dosing on Day 15 for 10 mg/cm^2 and 2 mg/cm^2 application rates respectively. The increase in percutaneous absorption upon multiple topical dosing was also observed in two previous clinical pharmacokinetic studies with psoriatic patients using the topical tazarotene gel formulation (Reports PK-95-048 and PK-97-004). However, the data also suggested that the steady state was reached by Day 8 for both cream application rates. The linear regression analysis (Table XIII, Figures 7 and

8) showed that the trough plasma tazarotenic acid concentrations did not change over time with a flat slope and a non-zero intercept. When comparing Days 8 and 15, the 95% confidence intervals (Table XIV) for C_{max} and AUC_{24} encompassed unity indicating that the respective parameters were similar for Days 8 and 15.

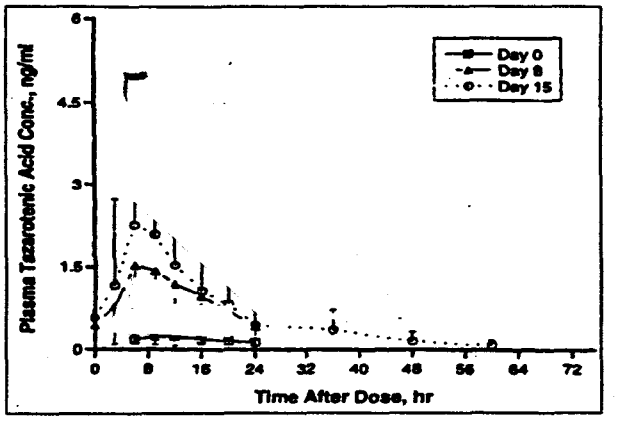

Figure 5: Mean plasma tazarotenic acid concentrations following once-daily administration of tazarotene cream 0.1% at 2 mg/cm^2 for 14 days to psoriatic patients.

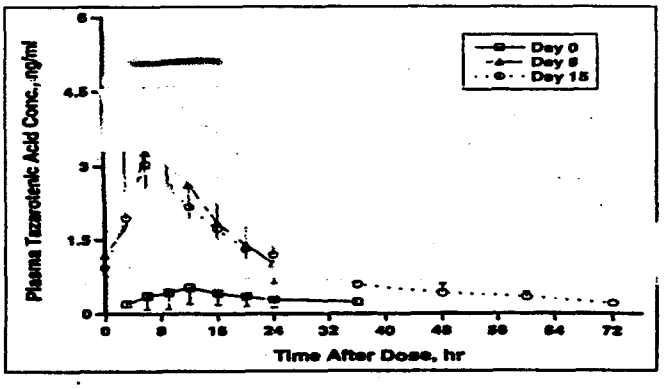

Figure 6: Mean plasma tazarotenic acid concentrations following once-daily administration of tazarotene cream 0.1% at 10 mg/cm^2 for 14 days to psoriatic patients.

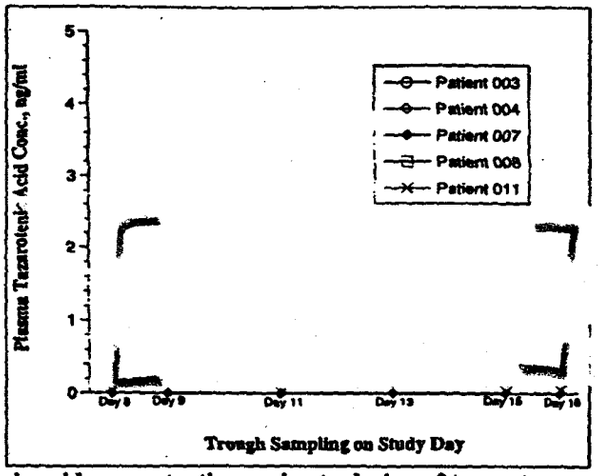

Figure 7: Plasma tazarotenic acid concentrations prior to dosing of tazarotene cream 0.1% at 2 mg/cm^2 on study days 8, 9, 11, 13, 15 and 16

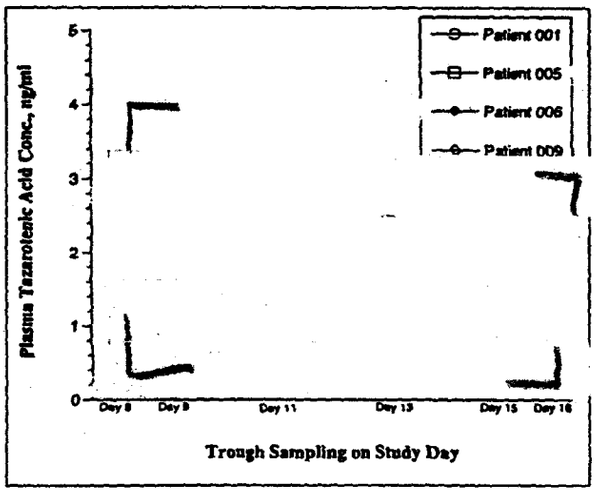

Figure 8: Plasma tazarotenic acid concentrations prior to dosing of tazarotene cream 0.1% at 10 mg/cm^2 on study days 8, 9, 11, 13, 15 and 16

Since the sample size was small for each dose group (N=4-5), direct statistical comparison of the bioavailability between the application rates would not be meaningful. However, the results appear to indiacte that the overall bioavailability of tazarotenic acid through the skin for the clinical application rate (2 mg/cm^2) was similar to that of the exaggerated dosing group (10 mg/cm^2).

The highest C_{max} and AUC_{24} values observed during this multi-dose study was 9.55 ng/mL and 141 ng.hr/mL, respectively, in an individual patient and at a dosing rate of 10 mg/cm^2 over 25% BA psoriatic involvement. The second highest C_{max} plasma tazarotenic acid concentration observed was 6.85 ng/ml with an AUC_{24} of 88.3 ng.hr/mL at 2 mg/cm^2 dosing rate over 36% BSA. However, on average, psoriatic patients in the two pivotal clinical efficacy trials (PK-99-044 and PK-99-060) had 11% body surface area of psoriatic involvement. Extrapolation of the results from this clinical pharmacokinetics study to 20% body surface area coverage, from the study mean

psoriatic involvement of 10%, yielded estimates for C_{max} of 6.04±1.09 ng/mL and AUC_{24} 98.4±18.6 ng.hr/mL. Given that the pharmacokinetic data were obtained from psoriatic patients treated at an application rate of 5 times (10 mg/cm^2) the normal clinical dosage of 2 mg/cm^2, the extrapolated C_{max} and AUC_{24} values represent good estimates of maximal human exposure after exaggerated dosages.

Table XIII: Linear Regression Analysis of Trough Plasma Tazarotenic Acid Concentrations on Days 8, 9, 11, 13, 15 and 16.

Patient Number	p-value[a] Intercept different from zero	Slope different from zero
Application Rate: 2 mg/cm^2 (n=5)		
003	0.0011	0.774
004	0.0093	0.364
007	NC[b]	NC
008	0.0019	0.572
011	0.0002	0.370
All Patients	0.0101	0.826
Application Rate: 10 mg/cm^2 (n=4)		
001	0.0002	0.438
005	0.0016	0.343
006	0.0245	0.0501
009	0.0243	0.458
All Patients	0.0073	0.923

[a] Statistically significant difference, $p \leq 0.05$.
[b] Not calculable, all values were below the limit of quantitation (BLQ).

Table XIV: Confidence Intervals of the Ratio of the Mean Pharmacokinetic Parameters of Tazarotenic Acid

Parameter	Ratio of Study Days	95% Confidence Intervals Application Rate 2 mg/cm^2	10 mg/cm^2
C_{max}	8/0	2.99 - 17.4	1.56 - 11.9
	15/0	4.49 - 19.6	2.49 - 10.2
	15/8	0.819 - 1.73	0.501- 2.72
T_{max}	8/0	0.375 - 1.06	0.464- 1.32
	15/0	0.375 - 1.06	0.384- 1.13
	15/8	0.648 - 1.73	0.606- 1.17
AUC_{24}	8/0	2.56 - 16.5	1.68 - 10.7
	15/0	4.02 - 15.7	2.84 - 8.70
	15/8	0.762 - 1.52	0.573- 2.39

Treatment related adverse events included those events rated by the investigator as possibly, probably, or definitely related to study medication. Overall 72.7% (8/11) patients experienced treatment-related adverse events. One or more treatment related adverse events were reported by 60.0% (3/5) of patients in the 2 mg/cm^2 dosage groups and 83.3% (5/6) of patients in the 10 mg/cm^2 dosage group. The majority of treatment-related events were rated as mild to moderate, and the distribution by severity was similar across the 2 dosage groups. Severe treatment related adverse events were reported by one patient in each dosage group. One patient in the 2 mg/cm^2 dosage group experienced severe pruritis. Only one patient in the 10 mg/cm^2 dosage group experienced and was discontinued due to severe pruritis and severe hypertension. The majority of treatment-

related adverse events were in the "skin and appendages" body system and included irritant contact dermatitis, pruritis, burning skin, and rash. Overall 72.7% (8/11) patients reported treatment related adverse events in this category [60.0% (3/5) of patients in the 2 mg/cm^2 dosage group and 83.3% (5/6) of patients in the 10 mg/cm^2 dosage group].

In conclusion, the systemic exposure (C_{max} and AUC_{24}) of tazerotenic acid after topical applications of tazarotene cream 0.1% at clinical (2 mg/cm^2) and exaggerated (10 mg/cm^2) dosing rates daily for 14 days in psoriatic patients were comparable. After multiple dosing, the mean systemic bioavailability from topical applications of tazarotene cream 0.1% is low, approximately 3% and 2% of the applied dose for 2 and 10 mg/cm^2 dosing rates, respectively.

Comments:

- The study did not include 0.05% cream formulation.
- The sponsor defined 10 mg/cm^2 as "exaggerated" dosing rate. However, to generate meaningful data from higher exposure (true exaggeration), the sponsor should have increased the area of exposure rather than applying thicker amount on the same surface area. As both 2 mg and 10 mg of creams were applied on the same surface area from the same formulation, significant change in systemic exposure was not expected anyway. Based on the formulation, application of excessive amount in limited area may sometimes reduce systemic bioavailability as found in this case that the bioavailability increased from 0.63% and 1.07% on Day 0 to 1.83% and 2.54% upon multiple dosing on Day 15 for 10 mg/cm^2 and 2 mg/cm^2 application rates respectively.
- In this multiple dose PK study, much higher plasma concentrations and bioavailability of the active metabolite were observed upon repeated dosing which leads to the possibilities of (a) some accumulation over time and/or (b) modification of skin permeability. However, as the data suggested, the rise in concentration plateaued around day 8 and stayed there.

Study VI. An Open-label, Single-Center, Pharmacokinetics Study of Tazarotene 0.1% Cream Applied Once Daily for 14 Days in the Treatment of Plaque Psoriasis (Study # 190168-024C) (August 7 – October 13, 1998) (Bioanalytical site and period November 2 – 15, 1999; Report Signed 1-21-00).

An identical study protocol as Study # 190168-023C (PK-99-085) was followed with nine patients (M=3, F=6). All of the 9 enrolled patients completed the study. However, pharmacokinetic analysis of plasma samples and analysis of efficacy data were not performed initially owing to a series of mistakes made by the investigational site in applying the assigned doses according to the schedule outlined in the protocol. The following narrative summarizes the protocol deviations observed in this study. Of the 9 patients enrolled, 8 were improperly dosed (only patient 009 was dosed per protocol). The two types of dosing errors that occurred during the study were: 1) site personnel did not recalculate the dose when patient's body surface area (BSA) involvement changed during the study, and 2) some doses were not accurately weighed by site personnel. Additional protocol deviations made by site personnel during the study occurred in treatment

assignments and timing of blood draws. Therefore the results of this study was not reviewed.

VIII: OVERALL CONCLUSIONS

Table XVI: Summary of In-Vivo Biopharmaceutics Studies

Report/Study /Date	Description	Treatment	Results	Comments
PK-99-044/ 190168-017C Study Period: 12/30/97-10/16/98 Report Date: 4/23/99	Multi-center, double-blind, randomized, vehicle-controlled, efficacy and safety in plaques psoriasis (n = 635: M=381; F=254) QD x 12 weeks	Tazarotene Cream 0.1% Tazarotene Cream 0.05% Vehicle Cream	Tazarotene was detected in the plasma in 2 of 69 drug-treated patients. The highest individual concentration was at ——— ——— Tazarotenic acid was detected in 42 of 69 patients. The highest individual concentration was at ———	Tazarotene creams 0.05% and 0.1% were demonstrated to be safe and have acceptable tolerability profiles.
PK-99-060/ 190168-016C Study Period: 12/29/97-01/22/99 Report Date: 6/7/99	Multi-center, double-blind, randomized, vehicle-controlled, efficacy and safety in plaques psoriasis (n = 668: M=434; F=234) QD x 12 weeks with 12 weeks post-treatment follow-up phase	Tazarotene Cream 0.1% Tazarotene Cream 0.05% Vehicle Cream	Tazarotene was detected in the plasma in 1 of 70 drug-treated patients. The highest individual concentration was at ——— ——— Tazarotenic acid was detected in 36 of 70 patients. The highest individual concentration was at ———	Tazarotene creams 0.05% and 0.1% were demonstrated to be safe and have acceptable tolerability profiles.
PK-99-085/ 190168-023C Study Period: 1/23/99-5/25/99 Report Date: 8/18/99	Multi-center, open-label, stratified by % psoriatic involvement to determine maximal exposure (n=11: M=4; F=7) QD x 14 doses	Tazarotene Cream 0.1% 2 mg cream/cm^2 or 10 mg cream/cm^2	Of 305 plasma samples from 9 completed patients, only 9 samples had measurable tazarotene with the highest at ——— Highest individual tazarotenic acid Cmax & AUC was ——— ——— The PK parameters for tazarotenic acid for the 2 dose groups are as follows: Dose (mg/cm^2) C_{max}(7-8h) (ng/mL) AUC (ng.hr/mL) 2 (n=5) 2.31±2.78 31.2±35.2 10 (n=4) 3.07±2.63 46.4±37.6	This represents a mean systemic bioavailability of 3 and 2% at 2 and 10 mg/cm^2, respectively.

In this submission, the sponsor is seeking an indication for the treatment of plaque psoriasis for Tazorac® (tazarotene topical cream) 0.05%, 0.1% which is a line extension of the previously approved Tazorac® (tazarotene topical gel) 0.05%, 0.1%.

The *in-vitro* skin permeation of tazarotene through human cadaver skin from cream formulations was studied. These data, along with data from animal toxicology, pharmacology and *in vivo* human skin irritancy studies, provided the basis for the

selection of the cream formulation for clinical trials. The ^{14}C-tazarotene skin distribution in pigs after topical dosing with radiolabelled tazarotene cream 0.1% demonstrated good drug delivery from the cream formulations into pig skin.

Overall summary of In-Vivo Biopharmaceutics Studies is described in Table XVI. From well-controlled pharmacokinetic studies where psoriatic patients were given tazarotene cream 0.1% under clinical and exaggerated dosing conditions, the systemic exposure was low, with a bioavailability of 2-3% of the topical dose. Under similar studies with 0.1% tazarotene gel, relatively higher C_{max}, AUC and systemic absorption were observed (Table XVII). Therapeutic drug monitoring of two pivotal efficacy studies confirm that chronic topical application of the tazarotene cream leads to limited systemic exposure. Systemic exposure of tazarotenic acid from cream increased after multiple dosing and plateaued around Day 8.

Table XVII: Quick Comparison of Gel and Cream Formulations

Formulation		Actual Parameters		Parameters Extrapolated to 20% BSA	
	BSA	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)
0.1% Gel (n = 5 psoriatics, 8-18% BSA 12 hr exposure without occlusion	13±5%	12±7.6 at 6 h	105±55 at 6h	18.9±10.6	172±88
0.1% Cream (n = 9 psoriatics, 5-35% BSA 12 hr exposure without occlusion	14±11%	2.31±2.78 at 8 h	31.2±35.2 at 8h	6.04±1.09*	98.4±18.6*

*Estimated at an exaggerated dosing regimen (10 mg/cm^2)

All these findings are comparable to findings obtained previously during submission of Tazorac® (tazarotene topical gel) 0.05%, 0.1% approved in June, 1997 and proven to be safe and effective topical treatment of retinoid responsive dermatoses.

IX: LABELING COMMENTS

Please refer to the **Pharmacokinetics** section under **Clinical Pharmacology** of proposed Tazorac® Cream labeling . ~~Strikeout~~ suggests deletion and shading suggests insertion.

/S/

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Pharmacokineticist
DPE III

Team Leader: E. Dennis Bashaw, Pharm.D. /S/ 7/31/00

CC: NDA 21-184 (Orig)
HFD-540/Div File
HFD-540/CSO/Bhatt
HFD-880(Bashaw/Ghosh)
HFD-880 (Lazor)
HFD-344 (Viswanathan)
CDR ATTN: B. Murphy