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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-184/S-001

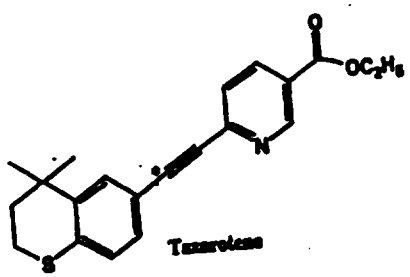
Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology/Biopharmaceutics Review

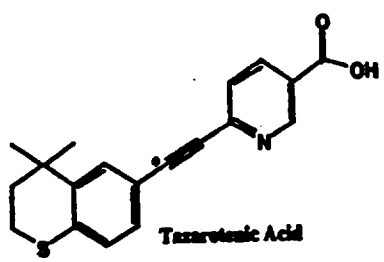
NDA:	21-184
SUBMISSION TYPE:	Efficacy Supplement (S001)
SUBMISSION DATE:	December 11, 2000
PRODUCT:	Tazorac® (tazarotene topical cream) 0.1%
INDICATION:	Acne vulgaris
SPONSOR:	Allergan, Inc., Irvine, CA 92623
REVIEWER:	Tapash K. Ghosh, Ph.D.

Synopsis

Tazarotene is a member of the acetylenic retinoids. It is intended for topical treatment of psoriasis and acne vulgaris. It is converted to its active form, tazarotenic acid, in biological systems by deesterification. The exact mechanism of action of this compound in acne is unknown. The anti-hyperproliferative, normalizing-of-differentiation and anti-inflammatory effects of tazarotene are considered the basis of its therapeutic effect in acne vulgaris.



Tazarotene



Tazarotenic Acid

Tazarotene 0.05% and 0.1% gels indicated for the topical treatment of stable plaque psoriasis and Tazarotene 0.1% gel indicated for the topical treatment of acne vulgaris were approved under NDA 20-600 in June, 1997. Tazarotene 0.1% Cream has recently been approved for plaque psoriasis on September 29, 2000.

In this application (NDA 21-184 S001), the sponsor seeks approval of 0.1% tazarotene cream formulation for the topical treatment of acne vulgaris. 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.

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.

Three clinical studies were conducted to evaluate safety and two out of these three also contain efficacy measurements to support approval of TAZORAC® (tazarotene) Cream, 0.1% in the once-daily treatment of acne-vulgaris. The findings from these studies are comparable to findings obtained previously during submission of Tazorac® (tazarotene topical gel) 0.05%, 0.1% gels approved in June, 1997 and TAZORAC® Cream 0.1% approved in September, 2000, and proven to be safe and effective topical treatment of retinoid responsive dermatoses.

Based on this review, NDA 21-184 S001 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 "Labeling Comments" and have been conveyed to the reviewing division.

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Clinical Pharmacology and Biopharmaceutics

A. Background:

Acne is a multifactorial disease. The four main factors involved in its development are excessive follicular keratinization, hyperactivity of the sebaceous gland, proliferation of *Propionibacterium acnes* and other microorganisms found in sebum-rich skin, and perifollicular inflammation. Acne is also a pleomorphic disease, characterized by different types and patterns of lesions and various stages of development. Acne vulgaris is the most common form of acne and is characterized by a mixture of inflammatory lesions (papules, pustules, and nodules) and non-inflammatory lesions (open comedones and closed comedones).

Although the exact mechanism of action remains undefined, retinoids are recognized as fundamental mediators of cell differentiation and proliferation. Tazarotene is a member of a novel class of retinoids, the acetylenic retinoids. Tazarotene, when administered either topically or systemically to hairless mice, is a potent inhibitor of TPA (phorbol 12-myristate 13-acetate)-induced ornithine decarboxylase activity, a classic measure of the anti-hyperproliferative activity of retinoids. The anti-hyperproliferative, normalizing-of-differentiation and anti-inflammatory effects of tazarotene are considered the basis of its therapeutic effect in acne vulgaris.

Tazarotene is thought to act against several of the factors that contribute to acne vulgaris, in either a direct or indirect manner. Its primary mechanisms of action are to normalize the keratinization pattern in acne and to decrease the coherence of follicular keratinocytes. This results in a comedolytic effect against existing comedones and prevents the development of new microcomedones. Tazarotene may also have direct and indirect activity against inflammatory acne. In skin rafts, it inhibits the expression of a presumed pro-inflammatory marker, migration inhibitory factor related protein type 8 (MRP8), suggesting a direct anti-inflammatory effect. It indirectly hinders the development of inflammatory acne by suppressing the microcomedo, the precursor acne lesion. In addition, by clearing obstructed follicles, tazarotene also allows aeration and release of accumulated sebum, making the follicles a less hospitable environment for P. acnes and indirectly halting the progression to inflammatory acne.

Tazarotene 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. 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%).

B. Summary of Previous Clinical Pharmacology experience with tazarotene *gel* in Acne

During clinical trials (NDA 20-600) for the treatment of facial acne, daily doses estimated to be 10 and 5 μg tazarotene/kg for the 0.1% and 0.05% *gels*, respectively was applied once daily for 12 weeks. Blood samples were drawn at 0-week, and weeks 8 and 12 for determination of plasma concentrations. Out of 92 drug treated patients who were sampled, 4% (4/92) had measurable tazarotene and 14% (13/92) had measurable active metabolite concentrations. Highest tazarotene and active metabolite concentrations were 0.22 and 0.15 ng/mL respectively.

In a recent pharmacokinetic study of tazarotene *gel* 0.1% after a single dose and after 6, 13, 26, and 40 repeat topical applications once daily over 15% body surface area in female patients with acne vulgaris, maximum exposure of tazarotenic acid occurred on study day 15. The C_{max} and AUC values (mean ± SD) on study day 15 were 4.8 ± 6.1 ng/ml and 44.6 ± 38.9 ng·hr/ml, respectively.

C. Summary of Current Clinical Pharmacology findings with tazarotene *cream* in Acne

After a single dose and after 6, 13, 20, and 27 repeat topical applications of tazarotene cream 0.1% once daily to either the face only or to an exaggerated body surface area (15%) in female patients with moderate to severe acne vulgaris (190168-035C):

- The maximum average C_{max} and AUC values of tazarotenic acid occurred on day 15 during a 29-day treatment for both the face only and the exaggerated dosing groups, and the single highest C_{max} throughout the study period was 1912 pg/mL on day 15 in the exaggerated dosing group.

- In the face only dosing group, the mean ± SD values of C_{max} and AUC_{0-24} of tazarotenic acid on day 15 were 104 ± 60 pg/mL (N = 8) and 1538 ± 1006 pg·hr/mL (N = 8), respectively.

- In the exaggerated dosing group, the mean ± SD values of C_{max} and AUC_{0-24} of tazarotenic acid on day 15 were 1200 ± 413 pg/mL (N = 10) and 17007 ± 6145 pg·hr/mL (N = 10), respectively.

- Mean C_{max} and AUC_{0-24} values of tazarotenic acid from patients in the exaggerated dosing group were more than 10 times higher than those from patients in the face only dosing group.

- The steady state pharmacokinetics of tazarotenic acid had been reached by day 8 in the face only and by day 15 in the exaggerated dosing group.

After topical application of either tazarotene cream 0.1% or tazarotene cream vehicle once daily for 12 weeks in 88 patients with facial acne vulgaris (190168-029C):

- The mean ± SD values of plasma tazarotenic acid at weeks 4 and 8 were not statistically different.
- The single highest observed plasma tazarotenic acid concentration throughout the study period was 406 pg/mL at week 4 from a female patient. The second highest plasma tazarotenic acid concentration throughout the study period was 197 pg/mL at week 4 in another female patient.
- Plasma tazarotenic acid concentrations appear to be independent of gender, age, body weight, and body surface area.
- No plasma tazarotenic acid concentrations were quantifiable in samples from the tazarotene cream vehicle treatment group.
- Efficacy outcome reveals marked improvement towards all clinical endpoints between active and vehicle groups. Improvement seemed to be better as the application period got longer (12 weeks > 8 weeks > 4 weeks).

D. Quick Comparison of Gel and Cream Formulations by Indications

Formulation	Indication	BSA	Parameters	
			C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)
0.1% Cream	Acne	15%	1.20±0.41	17.0±6.1
0.1% Gel	Acne	15%	4.84±6.05	44.6±38.9
0.1% Cream	Psoriasis	14±11%	2.31±2.78	31.2±35.2
0.1% Gel	Psoriasis	13±5%	12±7.6	105±55

Based on the above Summary Table the following conclusions were drawn:

- Compared to 0.1% Gel, 0.1% Cream always showed lesser systemic exposure under similar condition.
- Systemic exposure in acne is less than that in psoriasis from both Gel and Cream formulations
- Systemic exposure in acne is the least from 0.1% Cream formulation
- Plasma concentration did not correlate with the efficacy outcome which may be expected from topical therapy where improved efficacy may mean improvement of barrier function of the skin which leads to lower plasma concentration in subsequent weeks

E. Formulation

The following table describes the composition of the approved cream presently under consideration for new acne indication:

Ingredients	0.1% Cream (#9087X)
Tazarotene	0.10
Benzyl Alcohol	1.0
Sodium Thiosulfate, $5H_2O$ USP	
	-
	-
	-
Disodium EDTA	
Mineral Oil USP	
Medium Chain Triglycerides Ph Eur	
Carbomer 1342 NF	
Sorbital Monooleate NF	
	-
	-
Carbomer 934P	
	-
	-
	-
5N NaOH NF	

F. Pharmacokinetic Studies

The sponsor listed the following studies to provide ***in vivo*** pharmacokinetics data in support of 0.1% tazarotene cream for acne. The above formulation (#9087X) was used in all these studies. The first two studies are considered pivotal for this application whereas studies 3 and 4 are supportive. The studies have been reviewed individually and the reports have been included in the Appendix.

1. **Study 190168-035C-00**: *An open-label, single-center, parallel-group, pharmacokinetics study of tazarotene cream 0.1% after a single dose and after 6, 13, 20, and 27 repeat topical applications once daily to either the face only or to an exaggerated body surface area (15%) in female patients with acne vulgaris*

2. **Study 190168-029C-01**: *A multi-center, double-blind, randomized, vehicle-controlled, parallel-group study of the safety and efficacy of tazarotene cream 0.1% applied once daily for 12 weeks in patients with acne vulgaris*

3. **Study 190168-030-00**: *An open-label, multi-center, pharmacokinetics study of tazarotene gel 0.1% after a single dose and after 6, 13, 26, and 40 repeat topical applications once daily over 15% body surface area in female patients with acne vulgaris*

4. **Study 190168-022-01**: *An open-label, single-center, randomized, parallel-group pharmacokinetics study of tazarotene 0.1% gel qd, tazarotene 0.1% gel qod, tretinoin 0.1% cream qd, and adapalene 0.1% gel qd for one month in female patients with facial acne*

G. General Clinical Pharmacology Issues

- Tazarotenic acid is considered a weak inhibitor of cytochrom P450 enzyme with Ki values ranging from 4800 to 26000 ng/mL. Following topical dosing in humans, the tazarotenic acid concentration in plasma is several thousand times lower than these Ki values and therefore, the potential for a tazarotenic acid mediated drug-drug interaction is minimal.

- Being a topical dosage form, the characteristics of the exposure-response relationships for efficacy and safety is not defined. The therapeutic drug monitoring (190169-029C) had both PK and efficacy components. However, plasma concentration did not correlate with the efficacy outcome, which may be expected from topical therapy where improved efficacy may mean improvement of barrier function of the skin, which leads to lower plasma concentration in subsequent weeks.

H. Are the designs of the PK studies adequate to evaluate PK parameters and to demonstrate safety at the maximum usage condition to the right patient population?

Yes. Three clinical studies were conducted to evaluate safety and two out of these three also contain efficacy measurements to support approval of TAZORAC® (tazarotene) Cream, 0.1% in the once-daily treatment of acne-vulgaris. The findings from these studies are comparable to findings obtained previously during submission of Tazorac® (tazarotene topical gel) 0.05%, 0.1% gels approved in June, 1997 and TAZORAC® Cream 0.1% approved in September, 2000, and proven to be safe and effective topical treatment of retinoid responsive dermatoses.

LABELING COMMENTS

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

CLINICAL PHARMACOLOGY:

Tazarotene is a retinoid prodrug, which is converted to its active form, the cognate carboxylic acid of tazarotene (AGN 190299), by rapid deesterification in animals and man. AGN 190299 ("tazarotenic acid") binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ, and RARγ, but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of these findings is unknown. (FDA-approved text for tazarotene cream, psoriasis indication; see NDA 21-184.)

Psoriasis: The mechanism of tazarotene action 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 patients at high levels. In human keratinocyte cultures, it inhibits cornified envelope formation, whose build-up is an element of the psoriatic scale. Tazarotene also induces the expression of a gene which may be a growth suppressor in human keratinocytes and which may inhibit epidermal hyperproliferation in treated plaques. However, the clinical significance of these findings is unknown. (FDA-approved text for tazarotene cream, psoriasis indication; see NDA 21-184.)

Peris, K., M. C. Fargnoli, et al. (1999). Esgleyes-Ribot, T., R. A. Chandraratna, et al. (1994). Nagpal, S., S. M. Thacher, et al. (1996).

Pharmacokinetics:
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 was highly bound to plasma proteins (>99%). Tazarotene and tazarotenic acid were metabolized to sulfoxides, sulfones and other polar metabolites which were eliminated through urinary and fecal pathways.

In a multiple dose study with a once daily dose for 14 consecutive days in 9 psoriatic patients (male=5; female=4), measured doses of tazarotene 0.1% cream were applied by medical staff to involved skin without occlusion (5 to 35% of total body surface area: mean ± SD: 14 ± 11%). The Cmax of tazarotenic acid was 2.31 ± 2.78 ng/mL occurring 8 hours after the final dose, and the $AUC_{0\text{-}24\ h}$ was 31.2 ± 35.2 ng·hr/mL on day 15 in the five patients who were administered clinical doses of 2 mg cream/cm^2. (FDA-approved text for tazarotene cream, psoriasis indication; see NDA 21-184.)

During clinical trials with 0.05% or 0.1% tazarotene cream treatment for plaque psoriasis, three out of 139 patients with their systemic exposure monitored had detectable plasma tazarotene concentrations, with the highest value at 0.09 ng/mL. Tazarotenic acid was detected in 78 out of 139 patients (LLOQ = 0.05 ng/mL). Three patients . concentrations greater than 1 ng/mL. The highest value was 2.4 ng/mL. However, because of the variations in the time of blood sampling, the area of psoriasis involvement, and the dose of tazarotene applied, actual maximal plasma levels are unknown. (FDA-approved text for tazarotene cream, psoriasis

Draft

LABELING

/S/

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Team Leader: E. Dennis Bashaw, Pharm.D. _____

CC: NDA 21-184 (S001)
HFD-540/Div File
HFD-540/CSO/Bhatt
HFD-880(Bashaw/Ghosh)
HFD-880 (Lazor)

APPENDIX

NDA : 21-184 SN1/Study 190168-035C-00 Study Date: Jan'00- Feb' 00

AN OPEN-LABEL, SINGLE-CENTER, PARALLEL-GROUP, PHARMACOKINETICS STUDY OF TAZAROTENE CREAM 0.1% AFTER A SINGLE DOSE AND AFTER 6, 13, 20, AND 27 REPEAT TOPICAL APPLICATIONS ONCE DAILY TO EITHER THE FACE ONLY OR TO AN EXAGGERATED BODY SURFACE AREA (15%) IN FEMALE PATIENTS WITH ACNE VULGARIS

Objectives:

To evaluate the safety and pharmacokinetics of tazarotene cream 0.1% after a single dose and after 6, 13, 20, and 27 repeat topical applications once daily to either the face only or an exaggerated (15%) body surface area (BSA) in female patients with acne vulgaris.

Study Design:

Tazarotene cream 0.1% (9087X) was supplied in 100 gram tubes. For one group of 10 female patients with moderate or severe acne on their face, back, and chest, single and multiple-doses of tazarotene cream 0.1% were applied to the entire face (i.e., whole face from the mandibular line to the hairline edge), upper chest, upper back, and shoulders (the neck was optional depending on the patient's need) to a total area of approximately 15% body surface area (28 applications). In this exaggerated dosing group, a predetermined amount (2 mg/cm^2) of the study medication for each patient was weighed out in a weighing boat. A small pea-sized amount of cream was taken from the boat with the tip of a finger and spread evenly onto a section of the application area. Each dose was applied daily (except on Days 1 and 2) for 30 days This procedure was repeated until all the medication had been applied. The actual amount applied was recorded on the case report form.

For another group of 8 patients with moderate or severe acne present on their face at least, single and multiple-doses of tazarotene cream 0.1% (300 mg) were applied to the entire face only (i.e., whole face from the mandibular line to the hairline edge) (28 applications) in the same manner described above.

Doses were applied late afternoon/evening and washed off after 12 hours on the following day. Frequent blood samples were collected over 72 hours after the first dose, over 24 hours on days 8, 15, 22, and over 72 hours after the last dose (day 29).

Analytical Assay

Plasma tazarotenic acid (TA) concentrations were determined using a previously validated method with a lower limit of quantitation (LLOQ) at 5 pg/mL (Document: PK-95-044).

Results:

Tables 1a, 1b, 1c, 1d, and 1e present the list and summary of tazarotenic acid concentration values from patients in the face only dosing group at each sampling time on days 0, 8, 15, 22, and 29, respectively. Tables 2a, 2b, 2c, 2d, and 2e present the list and summary of tazarotenic acid concentration values from patients in the exaggerated dosing group at each sampling time on days 0, 8, 15, 22, and 29, respectively.

Mean ± SD plasma tazarotenic acid concentrations on days 0, 8, 15, 22, and 29 plotted as a function of time from patients in the face only dosing group and in the exaggerated dosing group are presented in Figures 1 and 2, respectively.

Table 1a: List and summary of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to the entire face on day 0, and at 3, 6, 9, 12, 16, 20, 24, 36, 48, 60, and 72 hours post-dose on days 0 to 2 from patients in the face only dosing group.

Patient	Days 0 to 2											
Number	0hr	3hr	6hr	9hr	12hr	16hr	20hr	24hr	36hr	48hr	60hr	72hr
1001	BLQ	15	28	31	25	21	18	14	8	BLQ	BLQ	BLQ
1003	BLQ	49	91	92	94	63	46	35	16	10	8	7
1005	BLQ	18	39	55	57	35	19	18	BLQ	BLQ	BLQ	BLQ
1007	BLQ	26	65	63	64	47	34	28	12	BLQ	BLQ	NR
1009	BLQ	21	43	39	43	33	30	19	12	BLQ	6	13
1011	BLQ	46	64	64	53	49	31	20	13	BLQ	BLQ	BLQ
1013	BLQ	33	93	143	108	69	45	40	25	10	20	BLQ
1015	BLQ	36	53	35	19	14	10	5	BLQ	BLQ	BLQ	BLQ
N	8	8	8	8	8	8	8	8	8	8	8	7
Mean	0	31	60	65	58	41	29	22	11	3	4	3
SD	0	13	24	37	31	19	13	11	8	5	7	5
CV	NA	42	40	57	53	47	44	51	77	185	168	181
Min												
Max												
Median	0	30	59	59	55	41	31	20	12	0	0	0

LLOQ = 5 pg/mL, BLQ = below lower limit of quantitation, NR = no reportable result, sample lost in wet lab, NA = not calculable

Table 1b: List and summary of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to the entire face on day 8, and at 3, 6, 9, 12, 16, 20, and 24 hours post-dose on day 8 from patients in the face only dosing group.

Patient	Day 8							
Number	0hr	3hr	6hr	9hr	12hr	16hr	20hr	24hr
1001	23	53	73	53	45	31	30	23
1003	30	121	137	174	137	88	79	57
1005	24	43	48	43	43	30	23	11
1007	48	131	149	108	75	57	52	30
1009	16	102	66	50	38	23	26	26
1011	22	61	87	72	54	28	32	22
1013	33	100	134	92	100	49	44	28
1015	6	25	28	25	18	11	11	6
N	8	8	8	8	8	8	8	8
Mean	25	80	90	77	64	40	37	25
SD	12	39	45	47	39	24	21	15
CV	49	49	50	62	61	61	57	60
Min								
Max								
Median	24	81	80	63	50	31	31	25

LLOQ = 5 pg/mL, NR = no reportable result, sample lost in wet lab, NA = not calculable

Table 1c: List and summary of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to the entire face on day 15, and at 3, 6, 9, 12, 16, 20, and 24 hours post-dose on day 15 from patients in the face only dosing group.

Patient	Day 15							
Number	0hr	3hr	6hr	9hr	12hr	16hr	20hr	24hr
1001	24	43	66	69	51	33	26	19
1003	44	145	173	166	148	148	93	66
1005	42	55	85	74	58	40	32	18
1007	23	136	140	114	98	59	52	33
1009	12	79	72	60	44	27	19	18
1011	14	40	56	42	35	22	14	10
1013	38	85	199	200	149	93	70	47
1015	8	29	27	12	12	10	9	BLQ
N	8	8	8	8	8	8	8	8
Mean	26	77	102	92	74	54	39	26
SD	14	44	61	64	52	46	30	21
CV	55	57	60	69	70	85	76	81
Min								
Max								
Median	24	67	79	72	55	37	29	19

LLOQ = 5 pg/mL, NR = no reportable result, sample lost in wet lab, NA = not calculable

Table 1d: List and summary of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to the entire face on day 22, and at 3, 6, 9, 12, 16, 20, and 24 hours post-dose on day 22 from patients in the face only dosing group.

Patient	Day 22							
Number	0hr	3hr	6hr	9hr	12hr	16hr	20hr	24hr
1001	13	43	68	56	41	28	19	16
1003	38	117	141	117	86	76	51	41
1005	26	63	82	66	66	41	32	20
1007	24	135	138	98	85	58	40	41
1009	16	79	83	66	47	30	23	20
1011	23	54	60	50	41	33	29	23
1013	30	58	111	107	79	54	48	30
1015	6	36	37	35	19	11	10	6
N	8	8	8	8	8	8	8	8
Mean	22	73	90	74	58	41	32	25
SD	10	35	37	29	25	20	14	12
CV	46	48	41	40	42	49	45	49
Min								
Max								
Median	24	61	83	66	57	37	31	22

LLOQ = 5 pg/mL, BLQ = below lower limit of quantitation, NR = no reportable result, sample lost in wet lab, NA = not calculable

Table 1e. List and summary of plasma tazarotenic acid concentrations (pg/mL) prior to topical application of tazarotene cream 0.1% to the entire face on day 29, and at 3, 6, 9, 12, 16, 20, 24, 36, 48, 60, and 72 hours post-dose on days 29 to 31 from patients in the face only dosing group.

Patient	Days 29 to 31											
Number	0hr	3hr	6hr	9hr	12hr	16hr	20hr	24hr	36hr	48hr	60hr	72hr
1001	13	45	82	38	44	34	27	21	10	7	BLQ	BLQ
1003	25	85	119	106	73	53	43	36	20	9	BLQ	BLQ
1005	18	73	60	60	61	37	21	16	7	BLQ	BLQ	BLQ
1007	20	56	85	60	56	49	42	31	18	6	BLQ	BLQ
1009	15	65	70	95	61	41	24	14	7	BLQ	BLQ	BLQ
1011	24	87	83	79	57	39	29	23	11	BLQ	BLQ	BLQ
1013	30	67	136	129	98	69	49	42	18	10	6	BLQ
1015	9	60	57	35	16	15	11	8	6	BLQ	BLQ	BLQ
N	8	8	8	8	8	8	8	8	8	8	8	8
Mean	19	67	87	75	58	42	31	24	12	4	1	0
SD	7	14	28	33	23	16	13	12	6	4	2	0
CV	36	21	32	44	40	37	42	49	47	111	283	NA
Min												
Max												
Median	19	66	83	70	59	40	28	22	11	3	0	0

LLOQ = 5 pg/mL, NR = no reportable result, sample lost in wet lab, NA = not calculable

Table 2a: List and summary of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to 15 % total body surface area on day 0, and at 3, 6, 9, 12, 16, 20, 24, 36, 48, 60, and 72 hours post-dose on days 0 to 2 from patients in the exaggerated dosing group.

Patient	Days 0 to 2											
Number	0hr	3hr	6hr	9hr	12hr	16hr	20hr	24hr	36hr	48hr	60hr	72hr
1002	BLQ	59	123	124	103	92	80	61	36	18	10	6
1004	BLQ	386	630	529	400	238	185	130	55	39	22	11
1006	BLQ	203	303	300	275	172	124	98	46	25	15	7
1008	BLQ	190	264	424	318	203	111	117	50	22	8	5
1010	BLQ	169	530	414	396	260	254	177	70	34	21	11
1012	BLQ	79	247	395	308	170	144	110	40	23	16	7
1014	BLQ	100	158	159	164	130	76	62	41	20	12	10
1016	BLQ	99	159	172	184	107	74	54	28	12	6	BLQ
1018	BLQ	139	229	341	392	225	144	101	49	26	14	9
1019	BLQ	92	273	304	235	224	185	139	58	35	18	12
N	10	10	10	10	10	10	10	10	10	10	10	10
Mean	0	152	292	316	278	182	138	105	47	25	14	8
SD	0	96	164	132	105	58	58	39	12	8	5	4
CV	NA	63	56	42	38	32	42	37	25	33	37	46
Min												
Max												
Median	0	120	256	323	292	188	134	106	48	24	15	8

LLOQ = 5 pg/mL, BLQ = below lower limit of quantitation, NR = no reportable result, sample lost in wet lab, NA = not calculable

Table 2b: List and summary of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to 15 % total body surface area on day 8, and at 3, 6, 9, 12, 16, 20, and 24 hours post-dose on day 8 from patients in the exaggerated dosing group.

Patient	Day 8							
Number	0hr	3hr	6hr	9hr	12hr	16hr	20hr	24hr
1002	112	594	611	444	343	232	190	143
1004	159	688	731	611	564	431	367	215
1006	88	479	676	584	396	324	288	182
1008	128	227	256	334	324	218	184	142
1010	192	730	888	794	673	472	313	326
1012	96	297	284	246	221	198	167	116
1014	114	380	433	393	433	255	201	142
1016	90	460	682	610	358	246	186	130
1018	179	390	458	545	449	291	206	136
1019	239	625	850	956	652	567	471	409
N	10	10	10	10	10	10	10	10
Mean	140	487	587	552	441	323	257	194
SD	51	168	221	213	147	125	100	98
CV	36	35	38	39	33	39	39	50
Min								
Max								
Median	121	470	644	565	415	273	204	143

LLOQ = 5 pg/mL, NR = no reportable result, sample lost in wet lab, NA = not calculable

Table 2c: List and summary of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to 15 % total body surface area on day 15, and at 3, 6, 9, 12, 16, 20, and 24 hours post-dose on day 15 from patients in the exaggerated dosing group.

Patient	Day 15							
Number	0hr	3hr	6hr	9hr	12hr	16hr	20hr	24hr
1002	166	1259	1096	825	633	423	394	297
1004	360	1396	1912	1526	1206	NR	677	427
1006	183	1149	942	778	763	551	376	279
1008	190	661	829	668	548	432	333	252
1010	374	1244	1631	1223	1000	888	710	542
1012	97	932	932	829	683	452	337	210
1014	13	896	886	812	586	348	208	164
1016	199	782	856	769	491	361	235	133
1018	124	757	813	616	469	323	243	185
1019	1047	1149	1718	1525	1236	851	696	479
N	10	10	10	10	10	9	10	10
Mean	275	1023	1162	957	762	514	421	297
SD	292	249	422	340	286	212	198	140
CV	106	24	36	36	38	41	47	47
Min								
Max								
Median	187	1041	937	819	658	432	357	266

LLOQ = 5 pg/mL, NR = no reportable result, sample lost in wet lab, NA = not calculable

Table 2d: List and summary of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to 15 % total body surface area on day 22, and at 3, 6, 9, 12, 16, 20, and 24 hours post-dose on day 22 from patients in the exaggerated dosing group.

Patient	Day 22							
Number	0hr	3hr	6hr	9hr	12hr	16hr	20hr	24hr
1002	193	1285	1658	1162	899	657	720	450
1004	368	1154	1737	1659	1088	1021	747	543
1006	129	548	658	567	421	314	291	167
1008	257	854	963	710	699	541	502	342
1010	148	892	1162	894	649	458	445	329
1012	170	631	897	698	508	450	316	300
1014	134	508	486	419	345	238	146	118
1016	233	1133	1223	995	907	690	416	298
1018	147	690	916	986	642	597	215	176
1019	319	1228	1561	1412	1170	1115	809	464
N	10	10	10	10	10	10	10	10
Mean	210	892	1126	950	733	608	461	319
SD	83	293	423	383	277	281	232	139
CV	39	33	38	40	38	46	50	44
Min								
Max								
Median	182	873	1063	940	674	569	431	315

LLOQ = 5 pg/mL, NR = no reportable result, sample lost in wet lab, NA = not calculable

Table 2e: List and summary of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to 15 % total body surface area on day 29, and at 3, 6, 9, 12, 16, 20, 24, 36, 48, 60, and 72 hours post-dose on days 29 to 31 from patients in the exaggerated dosing group.

Patient	Days 29 to 31											
Number	0hr	3hr	6hr	9hr	12hr	16hr	20hr	24hr	36hr	48hr	60hr	72hr
1002	202	1227	1513	1296	766	604	385	286	138	105	56	47
1004	314	1170	1635	1413	977	956	824	522	269	144	76	46
1006	230	896	1069	721	754	602	465	375	141	149	86	93
1008	157	690	810	724	661	530	240	250	74	123	74	42
1010	169	751	1110	852	577	487	425	406	109	161	60	58
1012	124	731	945	813	662	361	291	204	93	50	30	35
1014	96	651	636	486	474	326	168	137	88	65	40	39
1016	210	829	1012	984	723	436	326	240	128	81	62	61
1018	185	839	1108	1012	674	440	349	222	84	100	184	100
1019	346	926	1454	1395	888	736	618	422	266	149	121	93
N	10	10	10	10	10	10	10	10	10	10	10	10
Mean	203	871	1129	970	716	548	409	306	139	113	79	61
SD	78	194	317	313	144	189	192	120	72	39	45	25
CV	38	22	28	32	20	34	47	39	51	34	57	40
Min												
Max												
Median	194	834	1089	918	699	509	367	268	119	114	68	53

OQ = 5 pg/mL, BLQ = below lower limit of quantitation, NR = no reportable result, sample lost in wet lab, NA = not calculable

Figure 1: Mean±sd plasma tazarotenic acid concentration (pg/ml) – time (hours) profiles following topical application of tazarotene cream 0.1% the entire face on days 0, 8, 15, 22 and 29 from patients in the face only dosing group.

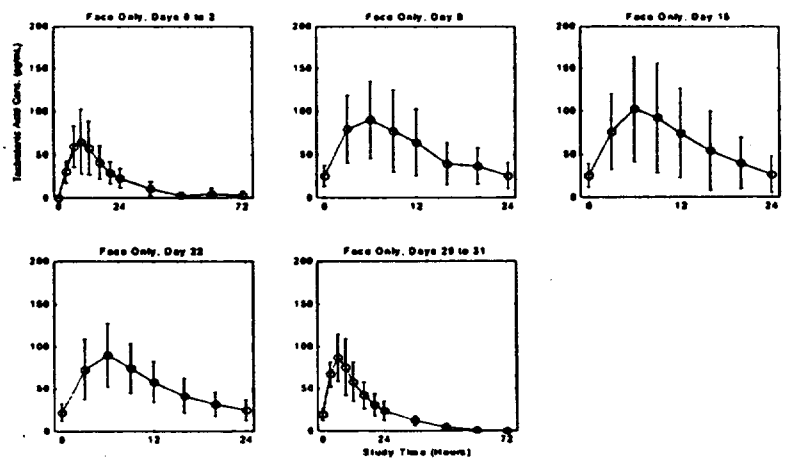
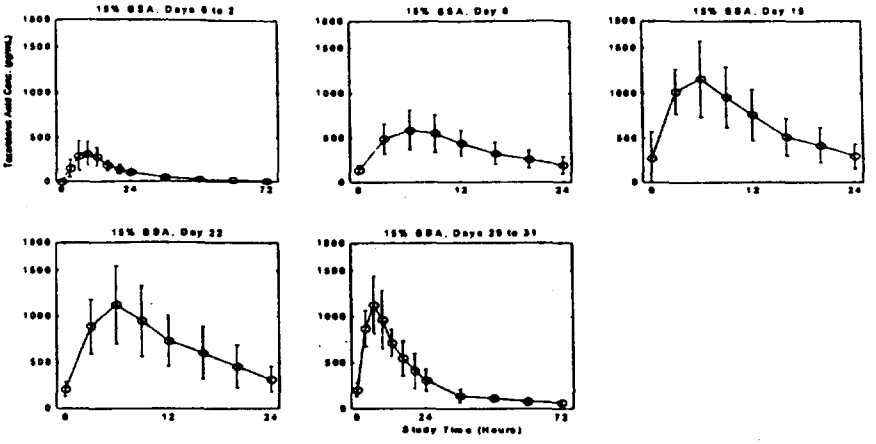


Figure 2: Mean±sd plasma tazarotenic acid concentration (pg/ml) – time (hours) profiles following topical application of tazarotene cream 0.1% to 15 % total body surface area on days 0, 8, 15, 22 and 29 from patients in the exaggerated dosing group.



The non-compartmental pharmacokinetic parameters of tazarotenic acid from patients in the face only dosing group and the exaggerated dosing group are presented in Tables I and II, respectively. The summaries of multivariate repeated-measures analyses of pharmacokinetic parameters C_{max} and AUC from patients in the face only dosing group and the exaggerated dosing group are also presented in Tables III and IV, respectively.

Table I. Mean ± SD pharmacokinetic parameters and trough concentrations of tazarotenic acid on study days 0, 8, 15, 22, and 29 from female patients with acne vulgaris following topical application of tazarotene cream 0.1% to the face only (N = 8)

Study Day	C_{max} ng/mL	C_{trough} ng/mL	AUC* ng•hr/mL	T_{max} hr	$T_{1/2}$ Hr
0	0.069 ± 0.035	BLQ	1.51 ± 0.79	8.3 ± 2.7	16.6 ± 13.1
8	0.099 ± 0.050	0.025 ± 0.012	1.36 ± 0.72	6.0 ± 1.6	NA
15	0.104 ± 0.060	0.026 ± 0.014	1.54 ± 1.01	6.0 ± 2.3	NA
22	0.090 ± 0.037	0.022 ± 0.010	1.29 ± 0.54	6.0 ± 0.0	NA
29	0.092 ± 0.025	0.019 ± 0.007	1.26 ± 0.40	5.3 ± 2.1	12.9 ± 3.6

*: $AUC_{0\text{-}inf}$ on day 1, and $AUC_{0\text{-}24}$ on days 8, 15, 22, and 29.
NA: Not Applicable
BLQ: Below quantification limit of 0.005 ng/mL

Table II. Mean ± SD pharmacokinetic parameters and trough concentrations of tazarotenic acid on study days 0, 8, 15, 22, and 29 from female patients with acne vulgaris following topical application of tazarotene cream 0.1% to 15% total body surface area (N = 10)

Study Day	C_{max} ng/mL	C_{trough} ng/mL	AUC* ng•hr/mL	T_{max} hr	$T_{1/2}$ Hr
0	0.345 ± 0.162	BLQ	6.64 ± 2.37	9.0 ± 2.4	14.7 ± 3.7
8	0.615 ± 0.219	0.140 ± 0.051	9.34 ± 3.24	6.6 ± 1.9	NA
15	1.20 ± 0.41	0.275 ± 0.292	17.0 ± 6.1	4.8 ± 1.5	NA
22	1.14 ± 0.42	0.210 ± 0.083	16.7 ± 6.4	6.0 ± 1.4	NA
29	1.13 ± 0.32	0.203 ± 0.078	16.2 ± 4.5	5.7 ± 0.9	18.1 ± 5.2

*: $AUC_{0\text{-}inf}$ on day 1, and $AUC_{0\text{-}24}$ on days 8, 15, 22, and 29.
NA: Not Applicable
BLQ: Below quantification limit of 0.005 ng/mL

Table III: Summary of multivariate repeated-measures analyses of pharmacokinetic parameters C_{max} and AUC from female patients in the face only dosing group

Comparison Group	p value (Probability > F)	
	C_{max}	AUC
Days 0, 8, 15, 22, and 29	p = 0.1105	p = 0.7135
Days 8, 15, 22, and 29	p = 0.6973	p = 0.7636
Days 15, 22, and 29	p = 0.5709	p = 0.5305

Table IV: Summary of multivariate repeated-measures analyses of pharmacokinetic parameters C_{max} and AUC from female patients in the exaggerated dosing group

Comparison Group	C_{max}	AUC
Days 0, 8, 15, 22, and 29	p = 0.0030	p = 0.0037
Days 8, 15, 22, and 29	p = 0.0017	p = 0.0016
Days 15, 22, and 29	p = 0.7390	p = 0.7495

Summary of C_{trough} values and plots of C_{trough} versus study days have been provided in Figures 3 and 4 for face only and exaggerated dosing groups respectively.

Figure 3: Box plot of plasma trough concentration profiles of tazarotenic acid on study days 8, 15, 22, and 29 from female patients with acne vulgaris following topical application of tazarotene cream 0.1% to the face only (N = 8).

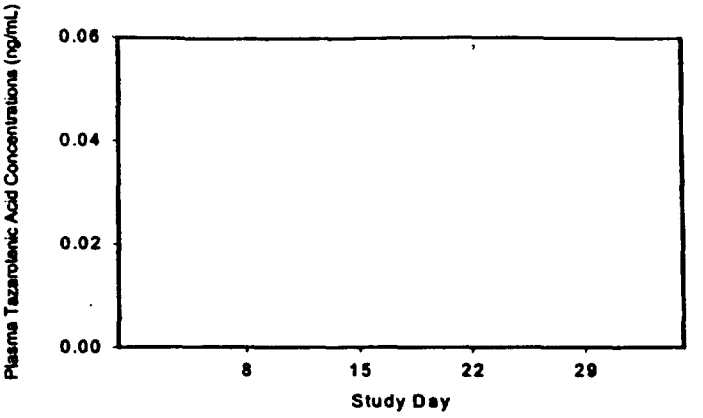
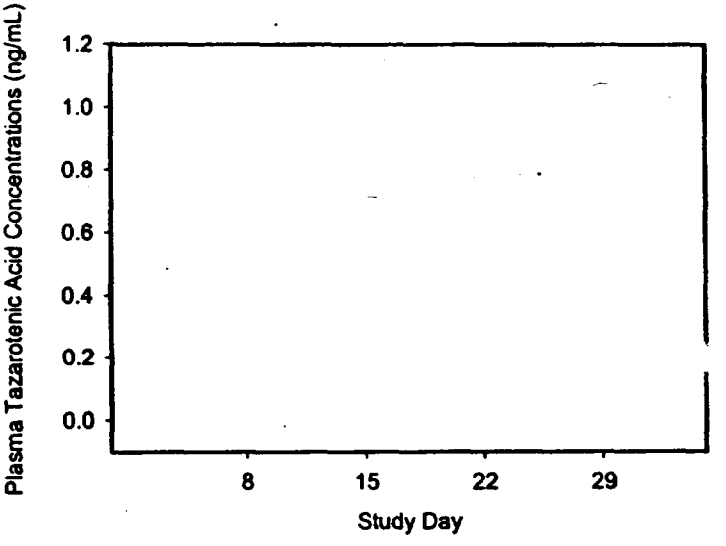


Figure 4: Box plot of plasma trough concentration profiles of tazarotenic acid on study days 8, 15, 22, and 29 from female patients with acne vulgaris following topical application of tazarotene cream 0.1% to 15% total body surface area (N = 10).



Note: *Box plots graph data as a box representing statistical values. The boundary of the box closest to zero indicates the 25th percentile, a line within the box marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. Whiskers (error bars) above and below the box indicate the 90th and 10th percentiles. Sometimes, outlying points will also show up.*

In general, when drug were applied to the face only, C_{trough} values are very low and are similar among days 8, 15, 22, and 29, suggesting that the steady state might have been reached by day 8. When drug were applied to the 15% body surface area, C_{trough} values

are usually similar among days 15, 22, 29 and 42, suggesting that the steady state might have been reached by day 15.

Discussion

Allergan conducted this clinical research study in order to determine the pharmacokinetic profile of tazarotenic acid after application of multiple doses (applied once daily) of tazarotene cream 0.1% to either the face only or an exaggerated (15%) body surface area in female patients with acne vulgaris. Because of the teratogenic risk associated with retinoids, females of child-bearing potential who might use tazarotene cream 0.1% for the treatment of acne vulgaris are a population of special concern. This current pharmacokinetic study was designed to provide the maximum pharmacokinetic information (following application to faces only as well as to an exaggerated body surface area of 15%) that would be relevant to that population.

Mean C_{max} and AUC_{0-24} values of tazarotenic acid from patients in the exaggerated dosing group were more than 10 times higher than those from patients in the face only dosing group. The single highest C_{max} throughout the study period was 1912 pg/mL on day 15 from one patient in the exaggerated dosing group.

There was no statistically significant difference in the mean values among pharmacokinetic parameters C_{max} and AUC on different study days from patients in the face only dosing group (Table III). There was no statistically significant difference in the mean values among pharmacokinetic parameters C_{max} and AUC on study days 15, 22, and 29 from patients in the exaggerated dosing group, indicating that the steady state pharmacokinetics of tazarotenic acid had been reached by day 15 (Table IV).

Conclusions:

After a single dose and after 6, 13, 20, and 27 repeat topical applications of tazarotene cream 0.1% once daily to either the face only or to an exaggerated body surface area (15%) in female patients with moderate to severe acne vulgaris:

1. The maximum average C_{max} and AUC values of tazarotenic acid occurred on day 15 during a 29-day treatment for both the face only and the exaggerated dosing groups, and the single highest C_{max} throughout the study period was 1912 pg/mL on day 15 in the exaggerated dosing group.

2. In the face only dosing group, the mean ± SD values of C_{max} and AUC_{0-24} of tazarotenic acid on day 15 were 104 ± 60 pg/mL (N = 8) and 1538 ± 1006 pg·hr/mL (N = 8), respectively.

3. In the exaggerated dosing group, the mean ± SD values of C_{max} and AUC_{0-24} of tazarotenic acid on day 15 were 1200 ± 413 pg/mL (N = 10) and 17007 ± 6145 pg·hr/mL (N = 10), respectively.

4. Mean C_{max} and AUC_{0-24} values of tazarotenic acid from patients in the exaggerated dosing group were more than 10 times higher than those from patients in the face only dosing group.

5. The steady state pharmacokinetics of tazarotenic acid had been reached by day 8 in the face only and by day 15 in the exaggerated dosing group.

Reviewer's Comments:

- *In reporting summary of multivariate repeated-measures analyses of pharmacokinetic parameters (Tables III and IV), C_{trough} data should be included along with C_{max} and AUC data to show that upon attaining steady state, it was maintained over the rest of the study..*

- *In both face only and exaggerated dosing groups, at least two (2) points (2/8 = 25% and 2/10 = 20%) were outliers at each time point (Figures 1 and 2). However, those data were used to compute the summary statistics for C_{trough}(Tables I and II). Statistical validity of such computation is questionable.*

- *Mean ± SD values of C_{max} reported in Tables I and II respectively do not match exactly from the source data reported in Tables 1 (a-e) and Tables 2 (a-e) respectively.*

APPEARS THIS WAY
ON ORIGINAL

NDA : 21-184 SN1/Study 190168-029C-01 Study Date: Sep' 99– Jun' 00

A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, VEHICLE-CONTROLLED, PARALLEL-GROUP STUDY OF THE SAFETY AND EFFICACY OF TAZAROTENE CREAM 0.1% APPLIED ONCE DAILY FOR 12 WEEKS IN PATIENTS WITH ACNE VULGARIS

Objectives:

To examine plasma tazarotenic acid (AGN 190299) concentrations at 3 to 10 hours after the morning dosing at weeks 4 and 8 through Therapeutic Drug Monitoring (TDM) and population pharmacokinetics.

Methods:

In this multi-center, double-blind, randomized, vehicle-controlled study, each patient with facial acne vulgaris applied either tazarotene cream 0.1% or tazarotene cream vehicle once daily for 12 weeks. Doses were applied to the face only daily in the late afternoon/evening and washed off after 12 hours on the following day. Blood samples were collected from 88 patients from five selected sites at 3 to 10 hours after the morning dosing at the week 4 and week 8 visits for determination of plasma tazarotenic acid concentrations. Plasma tazarotenic acid concentrations were determined using a validated GC/MS/MS method with a lower limit of quantitation (LLOQ) at 5 pg/mL. Efficacy outcome was measured at the end of 4, 8 and 12 weeks.

Results:

Population pharmacokinetic analyses were based on 48 patients (22 females and 26 males) in the tazarotene cream 0.1% treatment group, and from 40 patients (18 females and 22 males) in the tazarotene cream vehicle treatment group. No plasma tazarotenic acid concentrations were quantifiable in samples from the tazarotene cream vehicle treatment group.

A. Pharmacokinetics:

Plasma tazarotenic acid concentrations (pg/mL) from the tazarotene cream 0.1% treatment group were:

	Females and Males Combined		Females Only		Males Only	
	Week 4	Week 8	Week 4	Week 8	Week 4	Week 8
N	47	42	21	20	26	22
Mean	78	52	86	55	71	49
SD	73	37	96	41	49	34
CV (%)	94	71	112	74	68	68
Min						
Max						
Median	50	43	49	46	54	42

	Females and Males Combined Age 12-17 years		Females and Males Combined Age 18-44 years	
	Week 4	Week 8	Week 4	Week 8
N	27	25	20	17
Mean	65	51	95	54
SD	52	40	93	33
CV (%)	80	78	98	62
Min				
Max				
Median	46	38	66	46

There was no statistically significant difference (p values listed) for the following comparisons:

Statistical Comparisons	p-value	
	W[a]	t[b]
Between week 4 and week 8, males and females combined **(N = 41)**	0.0949	0.0628
Between week 4 and week 8, males only **(N = 22)**	0.0624	0.1064
Between week 4 and week 8, females only **(N = 19)**	0.6436	0.2522
Between males and females, week 4 **(N1 (female) = 21, N2 (male) = 26)**	0.5172	0.5069
Between males and females, week 8 **(N1 (female) = 20, N2 (male) = 22)**	0.8905	0.6001
Between age group of 12-17 and age group of 18-44, week 4 **(N1 (Age 12-17) = 27, N2 (Age 18-44) = 20)**	0.5149	0.1648
Between age group of 12-17 and age group of 18-44, week 8 **(N1 (Age 12-17) = 25, N2 (Age 18-44) = 17)**	0.4616	0.7686

[a] *Wilcoxon Signed-Rank Test*
[b] *One-Sample T-Test*

The results of linear regression analysis indicated that plasma tazarotenic acid concentrations are independent of body weight and body surface area.

Dependent Variable	Independent Variable	p-value for the slope
tazarotenic acid at week 4	body weight	0.3320 (N = 46)
tazarotenic acid at week 8	body weight	0.4005 (N = 41)
tazarotenic acid at week 4	body surface area	0.3125 (N = 46)
tazarotenic acid at week 8	body surface area	0.3880 (N = 41)

B: Efficacy Outcome:

The following results describe the efficacy outcome of the study:

Total Lesions - Median Percent Change From Baseline

Study week	Study 190168-029C		
	Taz 0.1% N=218	Vehicle N=218	P-value[a]
4	-21.51%	-14.52%	0.034
8	-36.27%	-20.93%	<0.001
12	-43.90%	-23.97%	<0.001

Taz = tazarotene cream. N = number of patients at baseline; subsequent sample sizes may vary due to missing values.

[a] *P-values based on two-way analysis of variance using a rank transformation*

Inflammatory Lesions - Median Percent Change From Baseline

Study week	Study 190168-029C		
	Taz 0.1% N=218	Vehicle N=218	P-value[a]
4	-16.33%	-14.29%	0.712
8	-29.71%	-23.21%	0.103
12	-40.69%	-27.43%	0.010

Taz = tazarotene cream. N = number of patients at baseline

[a] *P-values based on two-way analysis of variance using a rank transformation*

Non-Inflammatory Lesions - Median Percent Change From Baseline

Study week	Study 190168-029C		
	Taz 0.1% N=218	Vehicle N=218	P-value[a]
4	-20.57%	-13.89%	0.039
8	-39.36%	-21.68%	<0.001
12	-46.32%	-26.67%	<0.001

Taz = tazarotene cream. N = number of patients at baseline

[a] *P-values based on two-way analysis of variance using a rank transformation*

Incidence of "Clinical Improvement"[a]

Study week	Study 190168-029C		
	Taz 0.1% N=218	Vehicle N=218	P-value[a]
4	25.94%	22.64%	0.429
8	36.36%	26.70%	0.029
12	49.08%	33.49%	0.001

Taz = tazarotene cream. N = number of patients at baseline

[a] *Clinical Improvement defined as % of patients whose overall acne assessment improved by at least one grade from baseline.*

[b] *P-values based on Cochran-Mantel-Haenszel test*

Global Response to Treatment[a] - "Treatment Success"[b]

Study week	Study 190168-029C		
	Taz 0.1% N=218	Vehicle N=218	P-value[a]
4	24.06%	13.68%	0.004
8	44.98%	23.30%	<0.001
12	59.17%	33.94%	<0.001

Taz = tazarotene cream. N = number of patients at baseline

[a] *Completely cleared - 100% improved; almost cleared - approx. 90% improved; marked response - approx. 75% improvement; moderate response = approx. 50% improvement; slight response - approx. 25% improvement; condition unchanged; condition worsened*

[b] Treatment success defined as response of moderate, marked, almost cleared, or completely cleared

[c] *P-values based on Cochran-Mantel-Haenszel test*

Conclusions:

After topical application of either tazarotene cream 0.1% or tazarotene cream vehicle once daily for 12 weeks in 88 patients with facial acne vulgaris:

- The mean ± SD values of plasma tazarotenic acid at weeks 4 and 8 were not statistically different.
- The single highest observed plasma tazarotenic acid concentration throughout the study period was 406 pg/mL at week 4 from a female patient. The second highest plasma tazarotenic acid concentration throughout the study period was 197 pg/mL at week 4 in another female patient.
- Plasma tazarotenic acid concentrations appear to be independent of gender, age, body weight, and body surface area.
- No plasma tazarotenic acid concentrations were quantifiable in samples from the tazarotene cream vehicle treatment group.

- Efficacy outcome reveals marked improvement towards all clinical endpoints between active and vehicle groups. Improvement seemed to be better as the application period got longer (12 weeks > 8 weeks > 4 weeks).

Comments:

There was an apparent drop in plasma concentration between weeks 4 (78 ± 73 pg/mL) and week 8 (52 ± 37 pg/mL) of tazarotenic acid, though the drop was not found to be statistically significant (though the p value was bare marginal). However, it was found that efficacy improved as the period of application got longer (Week 12 > week 8 > week 4) though the sponsor did not run any statistical comparison among the efficacy outcomes based on number of weeks of application. It could be interesting to see if the efficacy outcomes were statistically different among weeks 4, 8 and 12. Nonetheless, plasma concentration did not correlate with the efficacy outcome, which may be expected from topical therapy where improved efficacy may mean improvement of barrier function of the skin, which leads to lower plasma concentration in subsequent weeks.

APPEARS THIS WAY
ON ORIGINAL

NDA : 21-184 SN1/Study 190168-030-00 **Study Date: Jul' 99 – Aug' 99**

AN OPEN-LABEL, MULTI-CENTER, PHARMACOKINETICS STUDY OF TAZAROTENE GEL 0.1% AFTER A SINGLE DOSE AND AFTER 6, 13, 26, AND 40 REPEAT TOPICAL APPLICATIONS ONCE DAILY OVER 15% BODY SURFACE AREA IN FEMALE PATIENTS WITH ACNE VULGARIS

Objectives:

To evaluate the safety and pharmacokinetics of tazarotene and tazarotenic acid (TA) under exaggerated use conditions after a single dose and after 6, 13, 26, and 40 repeat topical applications once-daily to females with moderate or severe acne vulgaris.

Study Design:

In this open-label, single-center, randomized, pharmacokinetics study, single and multiple-doses of tazarotene 0.1% gel, were applied to the entire face (i.e., whole face from the mandibular line to the hairline edge), upper chest, upper back, and shoulders (the neck was optional depending on the patient's need) to a total area of approximately 15% body surface area (41 applications) of female patients with moderate or severe acne vulgaris. Each dose was applied daily (except on Days 1 and 2) for 43 days. Doses were applied late afternoon/evening and washed off after 12 hours on the following day. Frequent blood samples were collected over 72 hours after the first dose, over 24 hours on Days 8, 15, 28, and over 72 hours after the last dose (Day 42). Plasma TA concentrations were determined using a validated [redacted] method with a lower limit of quantitation (LLOQ) at 5 pg/mL.

Results:

Summary of PK Parameters have been provided in the following Table I.

Table I: Mean ± SD pharmacokinetic parameters and trough concentrations of tazarotenic acid on study days 0, 8, 15, 28, and 42 from female patients with acne vulgaris following topical application of tazarotene 0.1% gel to 15% total body surface area (N = 13)

Study Day	C_{max} ng/mL	C_{trough} ng/mL	AUC* ng•hr/mL	T_{max} hr	$T_{1/2}$ Hr
0	0.289 ± 0.144	BLQ	6.55 ± 1.74	10.5 ± 3.2	15.8 ± 2.3
8	1.81 ± 1.70	0.243 ± 0.146	23.4 ± 19.5	6.3 ± 3.1	NA
15	4.84 ± 6.05	0.482 ± 0.338	44.6 ± 38.9	5.5 ± 1.1	NA
28	2.44 ± 1.81	0.309 ± 0.162	28.4 ± 19.8	5.8 ± 0.8	NA
42	1.95 ± 1.11	0.338 ± 0.186	24.8 ± 13.3	5.5 ± 1.7	19.6 ± 11.6

*: *AUC_{0-inf} on day 1, and AUC_{0-24} on days 8, 15, 28, and 42; NA: Not Applicable; BLQ: Below quantification limit of 0.005 ng/mL*

Maximum exposure of tazarotenic acid occurred on Study Day 15 during a 42-day treatment. The single highest C_{max} of 22751 pg/mL throughout the study period was from one patient on Study Day 15. Pharmacokinetic parameters C_{max} and AUC (AUC_{0-inf} on Day 1, AUC_{0-24} on Days 8, 15, 28 and 42) on Study Days 0, 8, 15, 28, and 42 were compared using the Wilcoxon-Signed-Rank Test. The mean TA C_{max} and TA AUC_{0-24} values on Study Days 8, 15, 28, and 42 were statistically significantly different from that on Study Day 0. However, there were no statistically significant differences for mean TA C_{max} and TA AUC_{0-24} values between Study Days 8 and 15, Study Days 8 and 28, Study Days 8 and 42, Study Days 15 and 28, Study Days 15 and 42, and between Study Days 28 and 42, indicating that steady state pharmacokinetics of tazarotenic acid had been reached by Day 8. There was no statistically significant difference for mean TA $T_{1/2}$ values between Study Days 0 and 42.

Comments:

- *Tazarotene 0.1% gel has already been approved for Acne vulgaris (NDA 20-6000). Rationale for conducting this current study with gel formulation is not clear while the sponsor in this submission has requested approval for Tazarotene 0.1% cream for acne indication.*

- *The sponsor stated in their report that "Maximum exposure of tazarotenic acid occurred on Study Day 15 during a 42-day treatment whereas they also showed that there were no statistically significant differences for mean TA C_{max} and TA AUC_{0-24} values between Study Days 8 and 15. These two statements are contradictory.*

NDA : 21-184 SN1/Study 190168-022-01 Study Date: Nov' 98 – Feb' 99

AN OPEN-LABEL, SINGLE-CENTER, RANDOMIZED, PARALLEL-GROUP PHARMACOKINETICS STUDY OF TAZAROTENE 0.1% GEL QD, TAZAROTENE 0.1% GEL QOD, TRETINOIN 0.1% CREAM QD, AND ADAPALENE 0.1% GEL QD FOR ONE MONTH IN FEMALE PATIENTS WITH FACIAL ACNE

Objectives:

- To determine the plasma concentration-time profiles of tazarotenic acid (tazarotene's active metabolite, TA), tretinoin and its metabolites (isotretinoin and oxoisotretinoin), and adapalene in female patients with mild to moderate facial acne.
- To compare the pharmacokinetic profiles of tazarotenic acid after daily and every other day dosing.

Study Design:

In this open-label, single-center, randomized, parallel-group pharmacokinetics study, single and multiple-doses of tazarotene (AGN 190168) 0.1% gel, adapalene 0.1% gel, and tretinoin 0.1% cream were applied to the entire face of female patients (16 to 43 years of age) with mild to moderate facial acne. In three different groups of 11, 10, and 10 patients, 72 hours after the first dose on Day 0, tazarotene 0.1% gel, adapalene 0.1% gel, and tretinoin 0.1% cream were applied once daily (QD) for 26 days, respectively. Frequent blood samples were collected over 72 hours after the first dose, and over 24 hours after the last dose (Day 28). In another group of 10 patients, 96 hours after the first dose on Day 0, tazarotene 0.1% gel was applied once-every-other-day (QOD) for 25 days. Frequent blood samples were collected over 72 hours after the first dose, and over 48 hours after the last dose (Day 28). Plasma TA and adapalene concentrations were determined using validated methods with lower limits of quantitation (LLOQ) at 5 and 10 pg/mL, respectively. Plasma tretinoin and its metabolites were assayed using a validated method with a LLOQ of 0.5 ng/mL. Non-compartmental pharmacokinetic parameters were calculated and summarized using descriptive statistics.

Results:

Tazarotene 0.1% Gel

Summary of PK parameters for tazarotenic acid applied QD and QOD regimens have been provided in the following Tables I and II respectively:

Table I. Mean ± SD pharmacokinetic parameters and trough concentrations of **tazarotenic acid** on study days 0, 8, 14, 22, and 28 from female patients with facial acne following facial application of tazarotene 0.1% gel once daily **(QD)** (N = 11)

Study Day	C_{max} ng/mL	C_{trough} ng/mL	AUC* ng•hr/mL	T_{max} hr	$T_{1/2}$ hr
0	0.051 ± 0.025	BLQ	0.935 ± 0.404	8.5 ± 2.6	11.9 ± 4.3
8	NA	0.013 ± 0.010	NA	NA	NA
14	NA	0.014 ± 0.011	NA	NA	NA
22	NA	0.017 ± 0.015	NA	NA	NA
28	0.136 ± 0.107	0.015 ± 0.010	1.58 ± 1.17	5.7 ± 1.6	NA

*: $AUC_{0\text{-}inf}$ on day 1, and $AUC_{0\text{-}24}$ on day 28; NA: Not Applicable; BLQ: Below quantification limit of 0.005 ng/mL

Table II. Mean ± SD pharmacokinetic parameters and trough concentrations of **tazarotenic acid** on study days 0, 8, 14, 22, and 28 from female patients with facial acne following facial application of tazarotene 0.1% gel once-every-other-day **(QOD)**(N = 10)

Study Day	C_{max} ng/mL	C_{trough} ng/mL	AUC* ng•hr/mL	T_{max} hr	$T_{1/2}$ hr
0	0.051 ± 0.046	BLQ	0.922 ± 1.01	9.3 ± 2.2	7.6 ± 2.2
8	NA	BLQ	NA	NA	NA
14	NA	BLQ	NA	NA	NA
22	NA	BLQ	NA	NA	NA
28	0.116 ± 0.105	BLQ	1.67 ± 1.41	7.5 ± 2.9	NA

*: $AUC_{0\text{-}inf}$ on day 1, and $AUC_{0\text{-}48}$ on day 28. NA: Not Applicable; BLQ: Below quantification limit of 0.005 ng/Ml

Adapalene 0.1% Gel

Summary of PK parameters for adapalene has been provided in the following Table III.

Table III. Mean ± SD pharmacokinetic parameters and trough concentrations of **adapalene** on study days 0, 8, 14, 22, and 28 from female patients with facial acne following facial application of adapalene 0.1% gel once daily (N = 10)

Study Day	C_{max} ng/mL	C_{trough} ng/mL	AUC* ng•hr/mL	T_{max} hr
0	0.035 ± 0.022	BLQ	0.451 ± 0.272	14.9 ± 5.9
8	NA	0.025 ± 0.018	NA	NA
14	NA	0.023 ± 0.030	NA	NA
22	NA	0.018 ± 0.025	NA	NA
28	0.045 ± 0.032	0.023 ± 0.024	0.637 ± 0.458	6.6 ± 5.1

*: $AUC_{0\text{-}72}$ on day 1, and $AUC_{0\text{-}24}$ on day 28;NA: Not Applicable; BLQ: Below quantification limit of 0.01 ng/mL

Tretinoin Cream 0.1%

Summary of PK parameters for tretinoin, isotretinoin, and oxoisotretinoin have been provided in the following Tables IV, V and VI respectively.

Table IV. Mean ± SD pharmacokinetic parameters and trough concentrations of **tretinoin** on study days 0, 8, 14, 22, and 28 from female patients with facial acne following facial application of tretinoin cream 0.1% once daily (N = 10)

Study Day	C_{max} ng/mL	C_{trough} ng/mL	$AUC_{0\text{-}24}$ ng•hr/mL	T_{max} hr
0	2.9 ± 0.3	2.6 ± 0.4	58.0 ± 9.5	15.6 ± 8.7
8	NA	2.4 ± 0.4	NA	NA
14	NA	2.3 ± 0.6	NA	NA
22	NA	2.3 ± 0.6	NA	NA
28	2.9 ± 0.4	2.6 ± 0.5	60.4 ± 9.9	12.7 ± 6.4

NA: Not Applicable;BLQ: Below quantification limit of 0.5 ng/mL

Table V. Mean ± SD pharmacokinetic parameters and trough concentrations of **isotretinoin** on study days 0, 8, 14, 22, and 28 from female patients with facial acne following facial application of tretinoin cream 0.1% once daily (N = 10)

Study Day	C_{max} ng/mL	C_{trough} ng/mL	$AUC_{0\text{-}24}$ ng•hr/mL	T_{max} hr
0	1.3 ± 0.9	1.1 ± 1.0	26.5 ± 21.2	13.6 ± 8.8
8	NA	1.2 ± 0.9	NA	NA
14	NA	1.0 ± 0.7	NA	NA
22	NA	1.1 ± 0.9	NA	NA
28	1.2 ± 0.7	1.1 ± 0.8	24.2 ± 18.2	6.9 ± 9.3

NA: Not Applicable; BLQ: Below quantification limit of 0.5 ng/mL

Table VI. Mean ± SD pharmacokinetic parameters and trough concentrations of **oxoisotretinoin** on study days 0, 8, 14, 22, and 28 from female patients with facial acne following facial application of tretinoin cream 0.1% once daily (N = 10)

Study Day	C_{max} ng/mL	C_{trough} ng/mL	AUC_{0-24} ng•hr/mL	T_{max} hr
0	1.9 ± 0.9	1.6 ± 0.8	40.4 ± 19.2	13.1 ± 7.0
8	NA	1.5 ± 0.6	NA	NA
14	NA	1.5 ± 0.6	NA	NA
22	NA	1.5 ± 0.5	NA	NA
28	1.6 ± 0.6	1.5 ± 0.6	35.2 ± 12.9	12.7 ± 3.4

NA: Not Applicable; BLQ: Below quantification limit of 0.5 ng/mL

Discussion:

Allergan conducted this clinical research study in order to determine the pharmacokinetic profile of tazarotenic acid, adapalene, tretinoin, and tretinoin metabolites after application of multiple doses of tazarotene 0.1% gel (applied either once daily or once every other day), adapalene 0.1% gel (applied once daily), and tretinoin 0.1% cream (applied once daily) to female patients with mild to moderate facial acne vulgaris. This study was expected to provide important data regarding the relative systemic exposure to tazarotene in comparison with two other marketed topical retinoids, namely tretinoin and adapalene. Females were used in this study because they represent a substantial segment of the acne population which is treated with topical retinoids, and the data were expected to have relevance vis a vis the concern regarding the teratogenic potential of retinoids. Every other day treatment with tazarotene was included among the treatment groups because this might be evaluated as a treatment option in the future. Based on previous Allergan studies and literature references, it was assumed that a 72 hours single dose interval would include at least 3 apparent elimination half-lives of tazarotenic acid, adapalene, tretinoin and its metabolites. Therefore, pharmacokinetic blood sampling over a 72 hours single dose interval would be adequate for the determination of single dose pharmacokinetic profiles of tazarotenic acid, adapalene, tretinoin and its metabolites. Previous studies also indicated that maximum drug exposure would occur in less than 28 days of dosing. The steady state might occur as early as study day 8. Pre-dose pharmacokinetic blood sample were taken on days 8, 14, and 22 to explore the attainment of steady state. From day 28, pharmacokinetic blood sample were taken over one dose interval of 24 hour for the QD dosing and 48 hours for the QOD dosing to determine the maximum drug exposure. The following summarizes the key findings of the study:

- The C_{max} and AUC values of tazarotenic acid over one dosing interval in both tazarotene 0.1% gel QD and QOD treatment groups are comparable.

- Tazarotenic acid concentrations after tazarotene 0.1% gel QD or QOD facial treatment are comparable to adapalene concentrations after adapalene 0.1% gel QD facial treatment in female patients with facial acne, and both tazarotenic acid and adapalene concentrations are much lower than endogenous levels of tretinoin, isotretinoin, and oxoisotretinoin.

- The tretinoin, isotretinoin, and oxoisotretinoin concentrations remained unchanged at endogenous levels after single and repeat dosing of tretinoin 0.1 % Cream QD treatment.

Comments:

- *For both tretinoin, isotretinoin and oxoisotretinoin, PK profile between Day 0 and Day 28 did not change much. However, for adapalene and tazarotene, Day 28 showed more than 1.5 fold increase in AUC and C_{max}. Whether it was due to change in skin permeability or accumulation is not clear.*

- *In absence of any established "Potency Rating" for retinoids and efficacy outcome, just comparable PK profile among different retinoids does not mean much.*

- *In order to have a valid comparison among the products, the sponsor should have chosen 0.1% tretinoin gel instead of 0.1% tretinoin cream used for this study.*

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