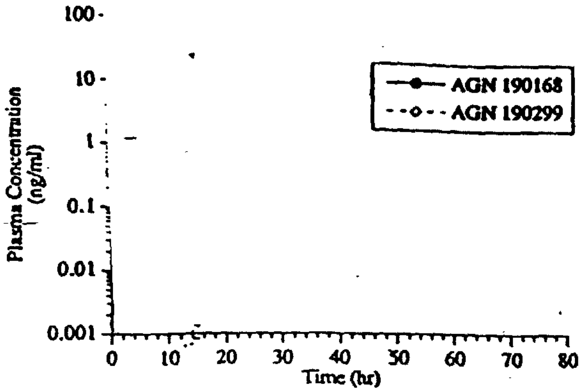
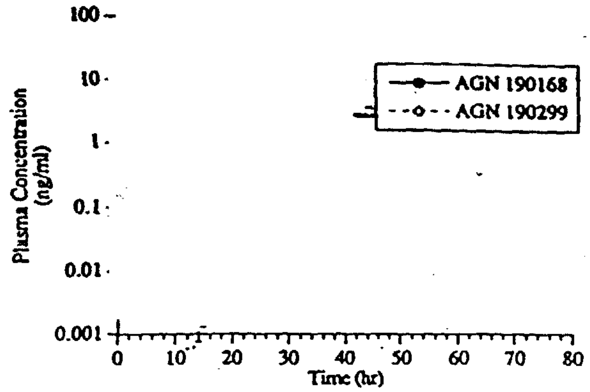
IV Infusion - Plasma Data

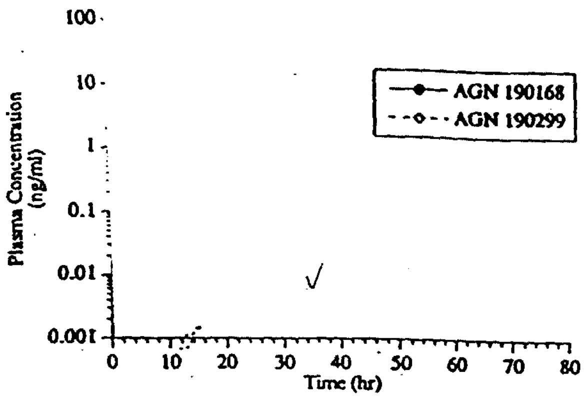
Subject [redacted]



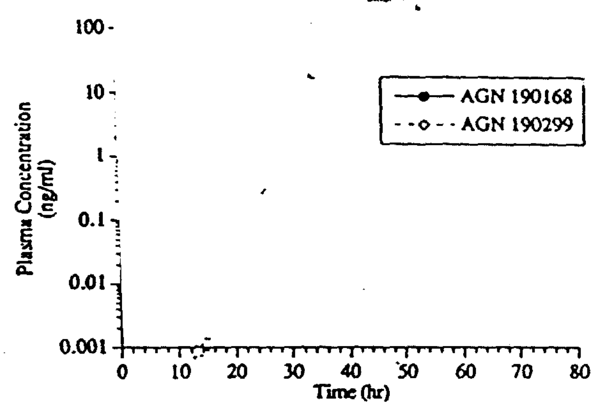
Subject [redacted]



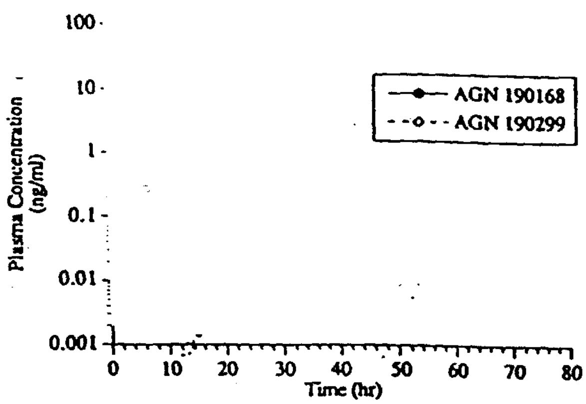
Subject [redacted]



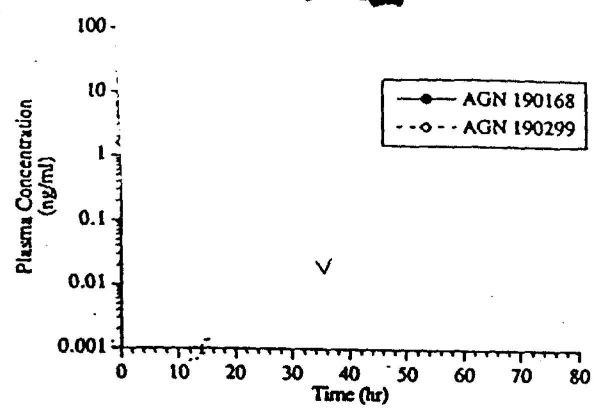
Subject [redacted]



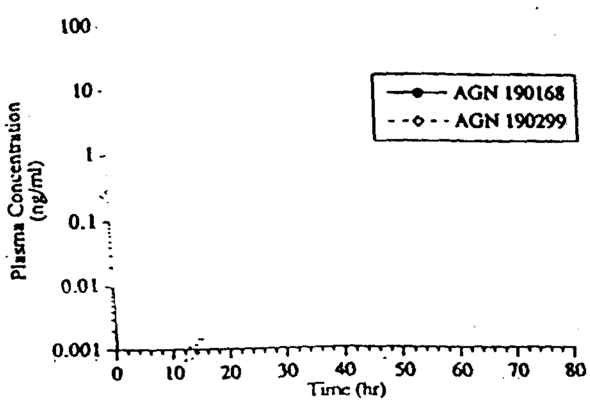
Subject [redacted]



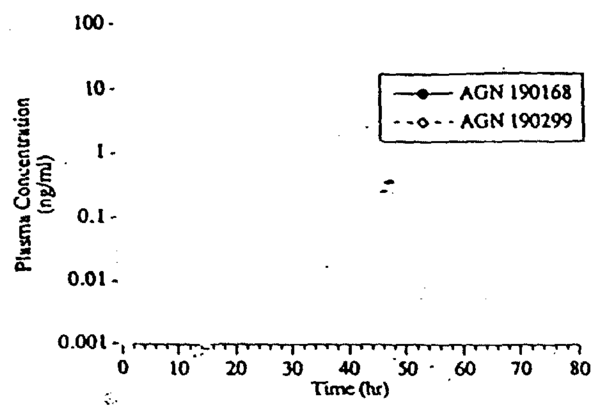
Subject [redacted]



Subject [redacted]

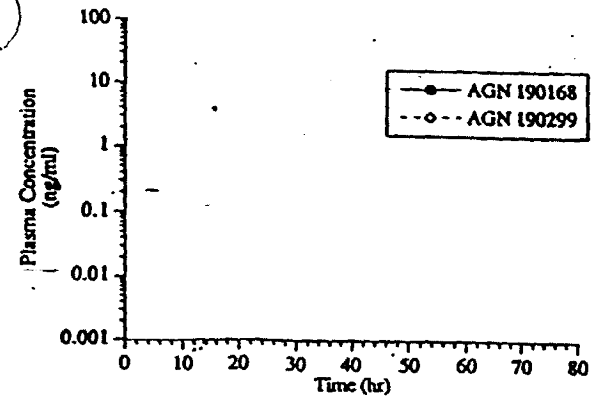


Subject [redacted]

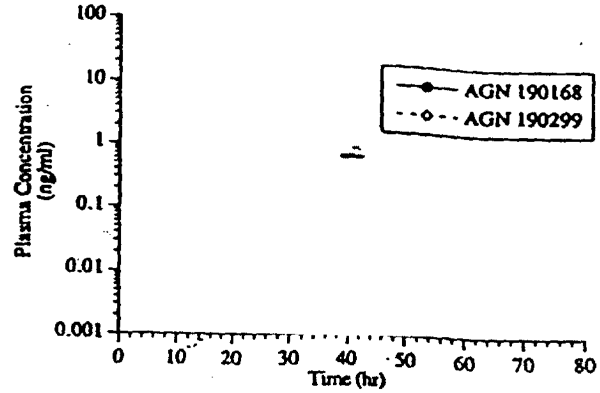


Topical Dose – Plasma Profile

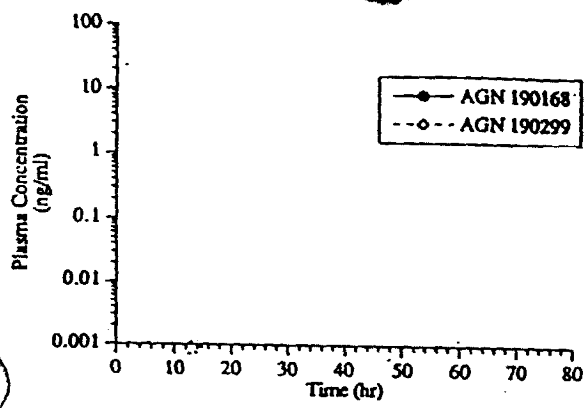
Subject [redacted]



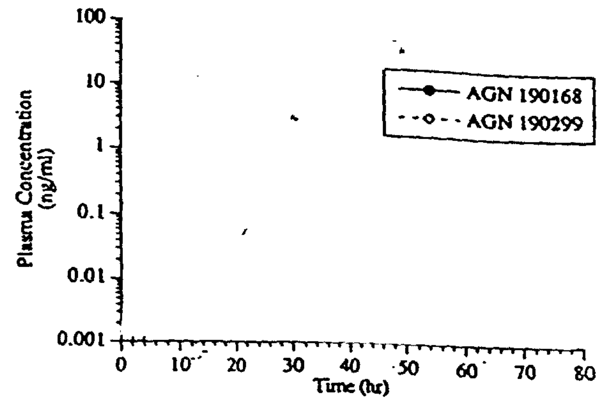
Subject [redacted]



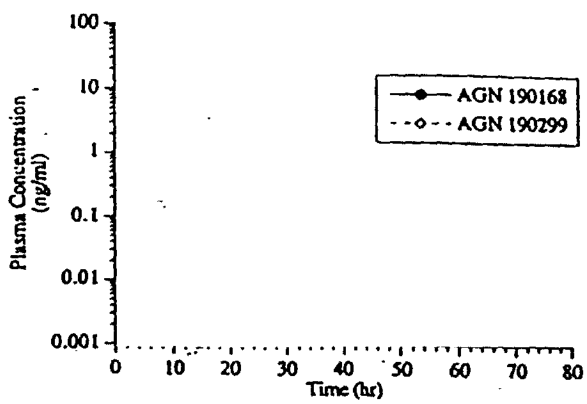
Subject [redacted]



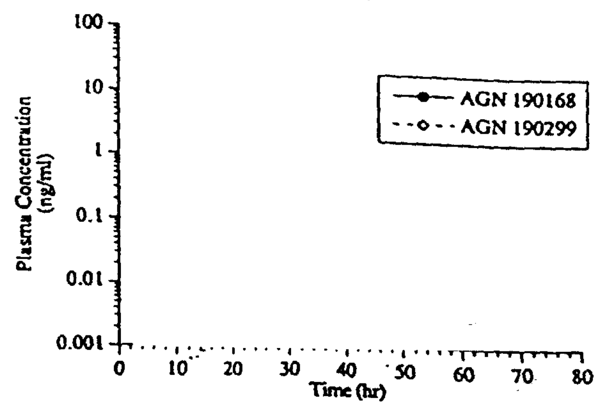
Subject [redacted]



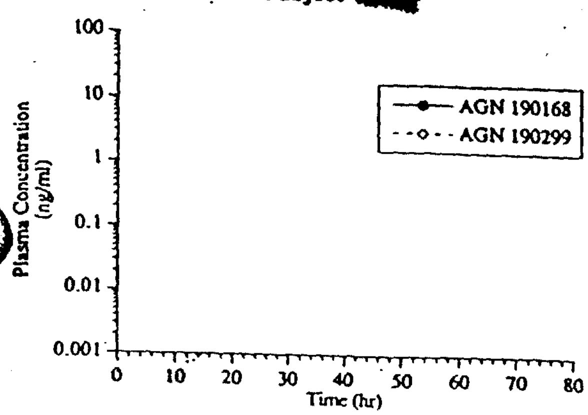
Subject [redacted]



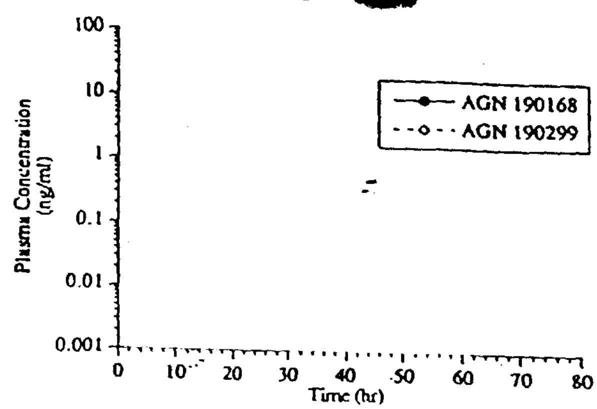
Subject [redacted]



Subject [redacted]



Subject [redacted]



8) Study R168-153-8606: (Volume 2.16)

PHARMACOKINETICS OF AGN190168 FOLLOWING SINGLE DOSE AND MULTIPLE DOSE TOPICAL ADMINISTRATION OF 0.1% GEL OR 0.05% GEL TO SUBJECTS WITH STABLE PLAQUE PSORIASIS

INVESTIGATOR AND LOCATION:

OBJECTIVES:

1. To determine the plasma concentration-time profile of tazarotene and the active metabolite, following single dose and multiple dose topical applications of tazarotene 0.1% gel or 0.05% gel to psoriatic patients.
2. To determine if changes in the severity of psoriasis associated with treatment are correlated with pharmacokinetic parameters.

FORMULATION: Formulation #8606X (0.1% gel)
The sponsor stated that due to difficulties in recruiting subjects, 0.05% gel was not studied.

STUDY DESIGN:
This is a two-center, two period, open-label study. Twenty subjects were to be assigned to receive either the 0.1% or 0.05% gel formulation. However, due to difficulties in enrolling subjects in a timely manner, only 5 subjects were enrolled and all subjects received 0.1% gel treatment. The affected psoriatic skin for these subjects (age: 36.6±8.8 yrs, wt: 81.6±15.0 kg) ranged % of their body surface area.

During period 1, each subject received a single topical dose applied to their psoriatic plaques except face and scalp (Dose 1). Period 2 started immediately following 72 hr blood collection for period 1. During period 2, each subject received daily applications for 13 consecutive evenings (Doses 2 through 14).

The dose was applied at 2 mg of gel per cm^2. After dosing, the application site remained uncovered for approximately 2 hr while the gel dried, and then was covered with standard nighttime clothing. Each dose was removed 12 hr after dosing. The subjects remained confined 72 hr following Doses 1 and 14, and 48 hours following Dose 8. The % total body surface area involved with psoriasis did not change over the course of the study and hence the dose remained the same in the study.

Sample collections -

i) Blood samples:

Dose 1:	pre-dose, 3, 6, 9, 12, 14, 17, 20, 24, 30, 36, 42, 48, 60 and 72 hr
Dose 7:	pre-dose
Dose 8:	pre-dose, 3, 6, 9, 12, 14, 17, 20 and 24 hr after application
Dose 12:	pre-dose
Dose 13:	pre-dose
Dose 14:	pre-dose, 3, 6, 9, 12, 14, 17, 20, 24, 30, 36, 42, 48, 60 and 72 hr

ii) Urine samples: 4 hr interval prior to the first dose, and
24 hr interval following the last dose.

iii) Feces samples: One sample collected after the last dose

All sample processing was performed under yellow light.

ASSAY:

Urine samples:

Feces samples: Not assayed due to lack of an appropriate method.

DATA ANALYSIS:

BLQ values were not included in mean plasma concentration statistics. The mean plasma and urine concentrations were not calculated if 50% or greater of the samples at any single sampling time were BLQ.

Distribution rate constant ($k_{distribution}$): The values were calculated by regression of the linear portion of the semi-logarithmic concentration versus time plot hour after the first and last doses).

Terminal elimination rate constant ($k_{terminal}$): The k value for each subject was calculated by regression of the linear portion of the semi-logarithmic concentration versus time plot (at various intervals for tazarotene and 36 to 72 hr for the active metabolite) for the 1st and last doses.

$T_{1/2}$: Mean values are reported as harmonic means and the corresponding standard deviations were calculated using a jackknife technique.

AUC and AUMC: calculated for each subject by the trapezoidal rule.

F: The bioavailability was calculated by using the AUC_{0-inf} value determined from an IV infusion dose in a previous study. The calculation assumes the dose is quantitatively metabolized from tazarotene to the active metabolite in both studies (IV infusion and current study). It also assumes constant clearance between doses and between studies.

MAT: The mean absorption time for tazarotene was calculated as follows:

$$MAT_{TAZ,TOP} = MRT_{MET,TOP} - MRT_{MET,INTR}$$

(MRT: Mean residence time; TAZ: Tazarotene; MET: Active metabolite; INTR: intrinsic)

Correlation of the PK parameters with changes in psoriatic scores was attempted using a full multivariate model.

RESULTS:

The area of psoriatic involvement to which the gel was applied ranged from cm², and the mean dose applied was 2.10±0.11 μg of tazarotene per cm² (or 65.6±28.9 μg of tazarotene per kg).

a) Plasma samples:

i) Tazarotene: After a single dose, plasma tazarotene concentrations were very low and reached a Cmax of 0.016±0.013 ng/mL at a Tmax of 4.5±1.7 hr. Concentrations then declined exponentially with a $t_{1/2}$ of hr to reach the ng/mL) by hr post-dose. The mean AUC_{0-inf} was 0.263±0.108 ng.hr/mL.

The trough levels preceding the 7th and 8th dose were essentially BLQ. After the 8th dose, concentrations rose to reach a Cmax of 0.154±0.092 ng/mL (8-fold increase over the 1st dose) at a Tmax of 4.8±1.6 hr post-dose. Plasma concentrations then declined with a $t_{1/2}$ of hr and reached hr post-dose.

The trough levels preceding the 12th, 13th and 14th doses were essentially BLQ except subject After the 14th (last) dose, a Cmax of ng/mL increase over the 1st dose) at a Tmax of hr post-dose. Plasma concentration then decreased with a $t_{1/2}$ of hr to reach hr post-dose. However, subject had detectable tazarotene concentrations in all samples after the last dose ng/mL at hr). The sponsor indicated that this was more of an assay noise because the concentrations moved up and down instead of a steady decline.

The AUC_{0-inf} values were 0.263±0.108, 0.989±0.471 and 1.14±0.44 ng.hr/mL after the 1st, 8th and 14th dose, respectively. Since the concentrations reached hrs, AUC_{0TLDC} values for the dose were used for the calculation of bioavailability which was determined to be %, % over the 1st dose) and % over the 1st dose) for the 1st, 8th and 14th doses, respectively.

The MRT values was 12.7 hr after 1st dose which decreased to 6.2 hr after the 8th dose and then to 5.5 hr after the 14th dose. However, the MRT value for some subjects could not be calculated.

ii) Active metabolite (AGN190299):
After the first dose, plasma concentrations increased to reach a Cmax of ng/mL at a Tmax of hr. Concentrations then declined biexponentially with a distribution $t_{1/2}$ of hr and a terminal $t_{1/2}$ of hr. The concentration decreased to ng/mL at hr post-dose, respectively.

The mean trough levels preceding the 7th and 8th doses were approximately ng/mL. After the 8th dose, a Cmax of ng/mL was reached at a Tmax of hr. The concentrations then declined with a distribution $t_{1/2}$ of hr.

The mean trough levels preceding the 12th, 13th and 14th doses ranged from 1.1 to 1.2 ng/mL. (The plasma concentration at 24 hr after the last dose was also in this range: ng/mL). After the 14th dose, plasma concentrations rose to achieve a Cmax of ng/mL at a Tmax of hr. Plasma concentrations then declined with a distribution and terminal $t_{1/2}$ of hr, respectively.

The $AUC_{0\text{-}inf}$ values were ng.h/mL after the 1st and 14th doses, respectively. The $AUC_{0\text{-}inf}$ for the 8th dose could not be accurately determined due to the limitation of sampling time. The $AUC_{0\text{-}24}$ values were ng.h/mL after the 1st dose, ng.h/mL after the 8th dose, and ng.h/mL after the last dose. The latter two values were 4.79 and 6.24 times of the $AUC_{0\text{-}inf}$ value after the 1st dose. Using the $AUC_{0\text{-}inf}$ value obtained from the IV infusion dose in a separate study, the bioavailability increased from % after the first dose to % after the 8th dose and then to % after the last dose.

The MRT was hr and hr for the 1st and last dose, respectively. Using the intrinsic MRT (6.2 hr) obtained following the IV infusion dose, the MAT of tazarotene was found to be hr after the 1st dose and hr after the last dose.

There was a marked difference in Cmax and AUC values between Dose 1 and Dose 8 or between Dose 1 and Dose 14. In contrast, only small degree of increase was observed between Doses 8 and 14. Analysis of trough plasma concentrations of Doses 7 through 14 gave results consistent with steady state being achieved.

b) Urine samples:
In urine samples collected over the 24 hr period after the last dose, only one sample had detectable tazarotene and another one sample had detectable active metabolite. All subjects had detectable AGN 190844 and the mean excretion in 24 hr period was 6.09±4.86% (range: %) of the dose.

c) Psoriatic evaluation
The changes from baseline for erythma, plaque elevation and scaling during the two-week treatment period were tested insignificant using the Wilcoxon Sign Rank test but were considered clinically relevant by the sponsor. Multivariate regression analysis show that greater increases in bioavailability were associated with smaller decreases in erythma, greater

decreases in plaque elevation and greater decreases in scaling over time. Larger decreases in plaque elevation were also correlated with higher Cmax values.

Adverse events: Cases of elevated triglycerides (Patient [redacted] and vasodilation (patient [redacted]) were considered probably related to the medication and Patient [redacted] reported local irritation (itching and burning).

Comments:

1. Comparing to the study conducted in healthy subjects, this study in 5 psoriatic patients shows much greater increases in Cmax and AUC values upon repeated dosing with a mean Cmax of 12.0 ± 7.6 ng/mL and mean $AUC_{0\text{-}24}$ of 105 ± 55 ng.h/mL after the 14th dose. The increase in Cmax and AUC was a result of increased bioavailability upon repeated dosing and not due to changes in elimination rate.

Large variations were observed among subjects which could not be accounted for by the difference in dose and suggested that skin condition was the most influential factor in determining the rate and extent of percutaneous absorption.

Although the true steady state may not be reached with chronic dosing due to change of skin condition by the medication, the concentrations of the active metabolite appear to reach a plateau by Dose 8.

The labeling should be revised to reflect the findings of this study.

2. $AUC_{0\text{-}inf}$ value obtained from a previous IV infusion dose was used to calculate the bioavailability of Doses 1, 8 and 14 in this study. Since these are parallel studies with different subjects, the bioavailability values calculated can only be deemed as rough estimates.

3. This study included one female patient and is the only PK study where female subjects were enrolled.

KEY RESULTS

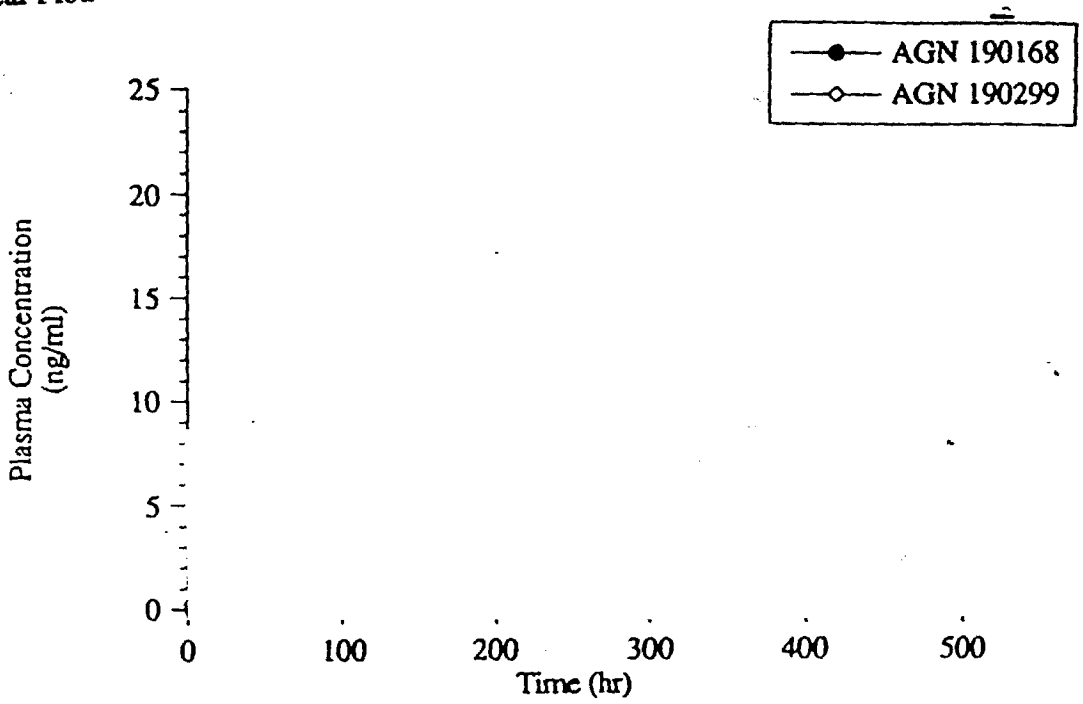
The psoriatic involvement ranged from 8% to 18% of total BSA with a mean of 12.7 ± 4.5%, and did not change over the study period. The mean dosage of AGN 190168 (only the 0.1% gel concentration was administered) was 65.6 ± 28.9 µg/kg and 2.10 ± 0.11 µg/cm^2. Mean (S.D.) of key results are presented as follows (n=5):

Parameter (Units)	AGN 190168			AGN 190299		
	Dose 1	Dose 8	Dose 14	Dose 1	Dose 8	Dose 14
C_{max} (ng/mL)	0.0162 (0.0133)	0.154 (0.092)	0.185 (0.084)	1.04 (0.94)	9.52 (7.49)	12.0 (7.6)
t_{max} (hr)	4.50 (1.73)	4.80 (1.64)	3.00 (0)	10.2 (2.7)	6.00 (0)	6.00 (2.12)
AUC_{0-24} (ng•hr/mL)	NC NC	NC NC	NC NC	14.8 (13.0)	89.7 (58.3)	105 (55)
AUC_{0-INF} (ng•hr/mL)	0.263 (0.108)	0.989 (0.471)	1.14 (0.44)	22.2 (19.1)	108 (76)	130 (67)
Terminal k (hr^{-1})	0.151 (0.114)	0.268 (0.082)	0.305 (0.021)	0.0378 (0.0079)	NC NC	0.0406 (0.0079)
Terminal $t_{1/2}$ (harmonic) (hr)	4.58 (4.89)	2.59 (0.83)	2.27 (0.16)	18.3 (3.8)	NC NC	17.1 (3.5)
Distribution k (hr^{-1})	NC NC	NC NC	NC NC	0.0757 (0.0174)	0.0869 (0.0232)	0.0814 (0.0134)
Distribution $t_{1/2}$ (harmonic) (hr)	NC NC	NC NC	NC NC	9.15 (2.10)	7.98 (2.08)	8.51 (1.44)
Bioavailability (% dose)	0.647 (0.023)	2.79 (1.77)	4.01 (1.70)	2.67 (1.44)	11.9 (5.9)	14.8 (7.6)
MAT_{168}^{skin}, hr	21.0 (6.6)	7.63 (2.00)	10.4 (1.6)	NA NA	NA NA	NA NA

NC = Not calculable
NA = Not applicable

Plasma Concentration Versus Time Profiles

Linear Plot.



Logarithmic Plot.

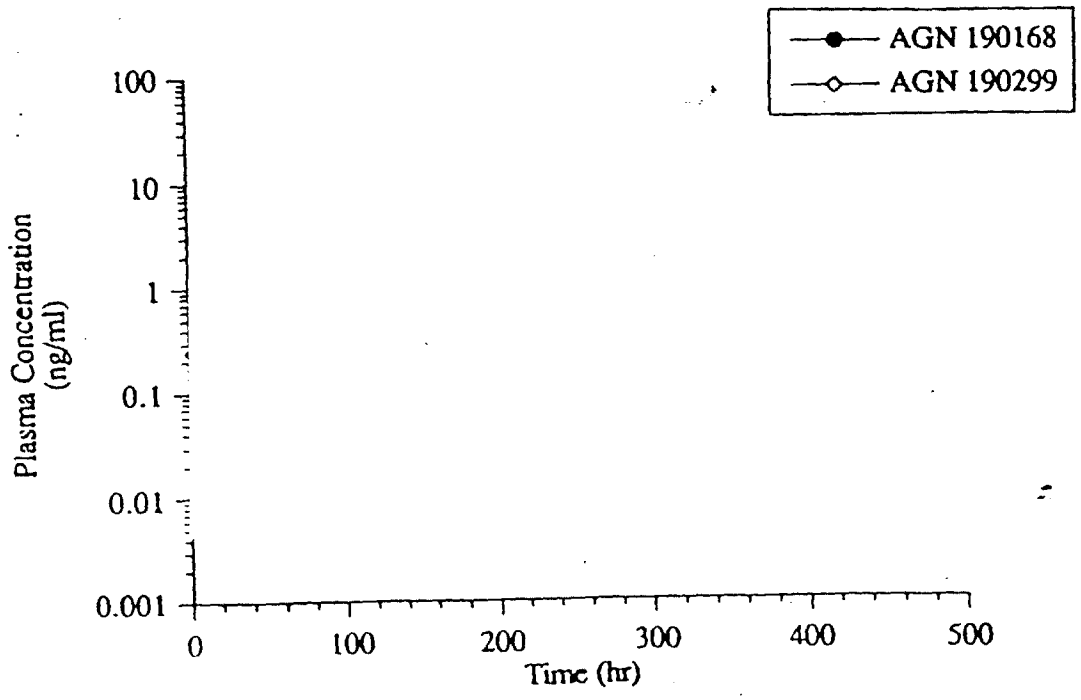


Table 9.1.2

Summary of Patient Characteristics: Height, Weight, Body Surface Area Involvement and Dosing Information

Patient	Height (m)	Weight (kg)	Body Surface Area (cm^2)	% Psoriatic Involvemt.	Dosed Area (cm^2)	Average Wgt Gel Dosed (g) [a]	Average AGN 190168 Dosage (µg/kg) [b]	Average AGN 190168 Dosage (µg/cm^2) [c]
N	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Mean	1.76	81.56	19740.00	12.67	2468.52	5.23	65.62	2.10
SD	0.12	15.01	2392.28	4.48	866.28	2.05	28.89	0.11
CV%	6.89	18.41	12.12	35.40	35.09	39.17	44.03	5.31

[a] Average weight of glove & wax paper before dosing minus after dosing.
[b] Average Dosage (µg/kg) = Average Wgt of AGN 190168 Dosed (µg) / Body Weight (kg).
[c] Average Dosage (µg/cm^2) = Average Wgt of AGN 190168 Dosed (µg) / Dosed Area (cm^2).

(KSTERN.R168151]R68153E1.SAS

Table 9.1.12

Patient Listing of Pre-Study Psoriatic Involvement and Severity

Patient	Percent of Psoriatic Involvement	Duration of Psoriasis (years)	Erythema Severity[a]	Plaque Elevation Severity[a]	Scaling Severity[a]
	16	24.0	2.0	2.5	3.0
	18	15.0	3.0	2.5	2.0
	10	23.8	2.0	1.5	2.5
	9	15.0	3.0	2.5	3.0
	8	11.0	4.0	2.5	4.0

[a] Severity scale: 0.0=None, 0.5=None+, 1.0=Mild, 1.5=Mild+, 2.0=Moderate, 2.5=Moderate+, 3.0=Severe, 3.5=Severe+, 4.0=Very Severe.

Table 9.1.13

Summary of Within-Study Psoriatic Involvement and Severity

Visit	N	Mean Psoriatic Involvement (%BSA)	Mean Erythema [a]	Mean Plaque Elevation [a]	Mean Scaling [a]
1.00	5	12.67 ± 0.0	2.80 ± 0.84	2.30 ± 0.45	2.90 ± 0.74
10.00	5	12.67 ± 0.0	2.40 ± 0.82	1.50 ± 0.35	1.20 ± 0.76
16.00	4	12.67 ± 0.0	2.50 ± 0.91	1.25 ± 0.50	1.38 ± 1.03

[a] Severity scale: 0.0=None, 0.5=None+, 1.0=Mild, 1.5=Mild+, 2.0=Moderate, 2.5=Moderate+, 3.0=Severe, 3.5=Severe+, 4.0=Very Severe.

Appendix 9.3.7 Pharmacokinetic Parameters of AGN 190168 by Subject, with Summary Statistics.

Parameter (Units)	Subject No. / Dose No.	Mean	S.D.	Range
C_{max} (ng/mL)	1	0.0162	0.0133	
	8	0.154	0.092	
	14	0.185	0.084	
t_{max} (hr)	1	4.50	1.73	
	8	4.80	1.64	
	14	3	0	
ΔC_{max} (ng/mL)	1	0.0162	0.0133	
	8	0.154	0.092	
	14	0.182	0.086	
terminal k (hr^{-1})	1	0.151	0.114	
	8	0.268	0.082	
	14	0.305	0.021	
terminal $t_{1/2}$ (hr) (harmonic)	1	4.58	4.89	
	8	2.59	0.83	
	14	2.27	0.16	
AUC_{0-24} (ng•hr/mL)	1	NC	NC	
	8	NC	NC	
	14	NC	NC	
AUC_{0-TLDC} (ng•hr/mL)	1	0.190	0.095	
	8	0.907	0.429	
	14	1.37	0.69	
AUC_{0-INF} (ng•hr/mL)	1	0.263	0.108	
	8	0.989	0.471	
	14	1.14	0.44	
$AUMC_{0-TLDC}$ (ng•hr^2/mL)	1	1.56	1.14	
	8	5.20	2.06	
	14	17.6	26.8	
$AUMC_{0-INF}$ (ng•hr^2/mL)	1	3.53	1.98	
	8	5.91	2.54	
	14	6.19	2.47	
F (% Dose)	1	0.647	0.023	
	8	2.79	1.77	
	14	4.01	1.70	
MRT^{168}_{TOP} (hr)	1	12.7	4.1	
	8	6.21	1.19	
	14	5.50	0.74	
MAT^{tin}_{168} (hr)	1	21.0	6.6	
	8	7.63	2.00	
	14	10.4	1.6	

NC = Not calculable

Appendix 9.3.8 Pharmacokinetic Parameters of AGN 190299 by Subject, with Summary Statistics.

Parameters (Units)	Subject No. / Dose No.	Mean	S.D.	Range
C_{max} (ng/mL)	1	1.04	0.94	
	8	9.52	7.49	
	14	12.0	7.6	
t_{max} (hr)	1	10.2	2.7	
	8	6.00	0	
	14	6.00	2.12	
ΔC_{max} (ng/mL)	1	1.04	0.94	
	8	8.38	6.64	
	14	10.7	7.0	
distribution k (hr^{-1})	1	0.0757	0.0174	(
	8	0.0869	0.0232	
	14	0.0814	0.0134	
distribution $t_{1/2}$ (hr) (harmonic)	1	9.15	2.10	
	8	7.98	2.08	
	14	8.51	1.44	
terminal k (hr^{-1})	1	0.0378	0.0079	(
	8	NC	NC	
	14	0.0406	0.0079	(
terminal $t_{1/2}$ (hr) (harmonic)	1	18.3	3.8	
	8	NC	NC	
	14	17.1	3.5	
AUC_{0-24} (ng.hr/mL)	1	14.8	13.0	
	8	89.7	58.3	
	14	105	55	
AUC_{0-TLDC} (ng.hr/mL)	1	21.0	18.1	
	8	NC	NC	
	14	126	66	
AUC_{0-INF} (ng.hr/mL)	1	22.2	19.1	
	8	108	76	
	14	130	67	
$AUMC_{0-TLDC}$ (ng.hr.hr/mL)	1	432	376	
	8	845	522	
	14	1770	871	
$AUMC_{0-INF}$ (ng.hr.hr/mL)	1	552	480	
	8	1565	1321	
	14	2119	1370	
F (% Dose)	1	2.67	1.44	
	8	11.9	5.9	
	14	14.8	7.6	
MRT^{299}_{TOP} (hr)	1	27.2	6.6	
	8	13.8	2.0	
	14	16.6	1.6	

NC = Not calculable

Table 9.1.8 % Dose Excreted into Urine Over a 24 Hour Period After the Last Dose (Dose 14) as AGN 190168, AGN 190299, AGN 190832 and AGN 190844

Compound	Mean	S.D	CV%
AGN 190168	NC	NC	NC
AGN 190299[a]	NC	NC	NC
AGN 190832[a]	NC	NC	NC
AGN 190844[a]	6.08	4.86	79.9
TOTAL	6.09	4.86	79.9

[a] = Reported as AGN 190168 equivalents
BLQ = Below limit of quantitation (1.0 ng/mL)
NC = Not calculable

Table 9.1.15 Correlation of Pharmacokinetic Parameters of AGN 190299 with Severity of Psoriasis by Stepwise Multivariate Regression Analysis

Best fit regression	p-value	R^2	Comments
F = 5.7955 + 7.9299*CHGERY - 4.7734*CHGPLQ - 0.3978*SCADOSE	0.0003	0.9713	No other regressors were necessary
$AUC_{0\text{-}24}$ = - 9.2926 - 117.3672*CHGPLQ	0.0030	0.7378	No other regressors were necessary
C_{max} = - 3.5007 - 15.7006*CHGPLQ	0.0029	0.7409	No other regressors were necessary
ΔC_{max} = - 3.5094 - 14.4433*CHGPLQ	0.0021	0.7639	No other regressors were necessary
t_{max} could not be fitted	N/A	N/A	All subjects had the same t_{max} for Dose 8
MRT = 10.4853 + 0.4182*DOSE	0.0850	0.3647	Model is not significant

where
CHGERY is the change in erythema from baseline
CHGPLQ is the change in plaque from baseline
CHGSCA is the change in scaling from baseline
DOSE represents dose 8 or 14
ERYDOSE is the interaction of change in erythema and dose
PLQDOSE is the interaction of change in plaque and dose
SCADOSE is the interaction of change in scaling and dose

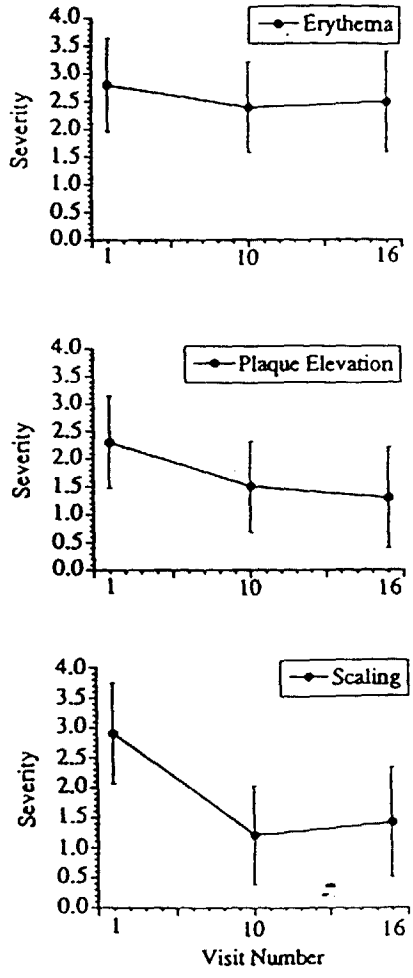


Figure 9.2.3 The Severity of Erythema, Plaque Elevation and Scaling Assessed Prior to Doses 1, 8 and 14 versus Time. (Mean ± S.D., n=4-5).

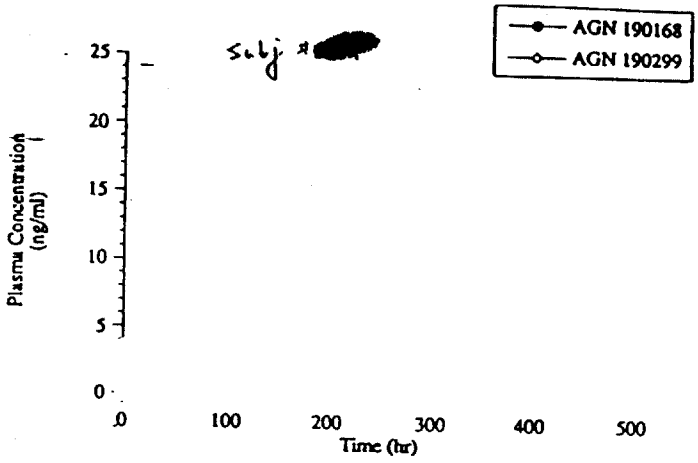
Appendix 9.3.3 Listing of Plasma Concentrations (ng/mL) versus Time of AGN 190168 by Subject, with Summary Statistics

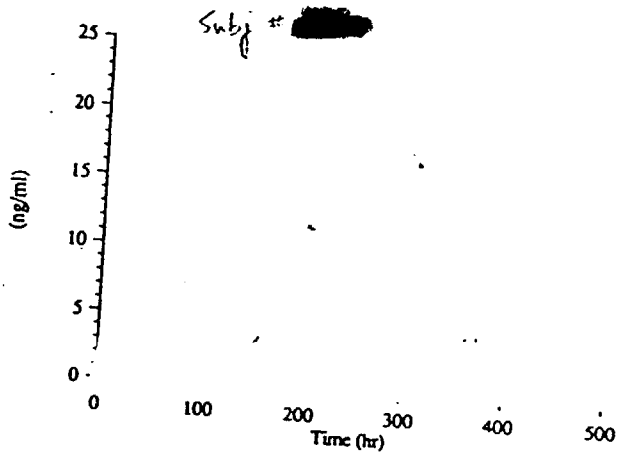
Dose No.	Time Since Preceding Dose (hr)	Cumulative Time Since Start (hr)	Subject No.	Mean	S.D.	CV%	Minimum	Maximum
1	0	0		NC	NC	NC	NC	NC
	3	3		0.0106	0.00503	47.4	0.00619	0.0161
	6	6		0.0239	0.00939	39.3	0.0131	0.0301
	9	9		0.0152	0.00595	39.0	0.0117	0.0221
	12	12		0.0118	0.00835	70.6	0.00557	0.0213
	14	14		NC	NC	NC	0.0122	0.0122
	17	17		NC	NC	NC	0.00759	0.00759
	20	20		NC	NC	NC	0.00763	0.00763
	24	24		NC	NC	NC	NC	NC
	30	30		NC	NC	NC	NC	NC
	36	36		NC	NC	NC	NC	NC
	42	42		NC	NC	NC	NC	NC
	48	48		NC	NC	NC	NC	NC
	60	60		NC	NC	NC	NC	NC
	72	72		NC	NC	NC	NC	NC
7	24	192		NC	NC	NC	0.00708	0.00708
8	24	216		NC	NC	NC	NC	NC
	3	219		0.147	0.0999	68.2	0.0341	0.292
	6	222		0.0966	0.0469	48.6	0.0473	0.157
	9	225		0.0271	0.0155	57.3	0.00759	0.0394
	12	228		0.0176	0.00797	45.3	0.00896	0.0294
	14	230		0.0108	0.00502	46.5	0.00563	0.0159
	17	233		0.0257	0.0290	113	0.00627	0.059
	20	236		NC	NC	NC	0.00625	0.00625
	24	240		NC	NC	NC	0.00857	0.00857
12	24	312		NC	NC	NC	0.00578	0.00578
13	24	336		NC	NC	NC	0.0235	0.0235
14	24	360		NC	NC	NC	0.0137	0.0137
	3	363		0.185	0.0837	45.4	0.067	0.273
	6	366		0.102	0.0486	47.5	0.062	0.175
	9	369		0.0383	0.0174	45.4	0.0216	0.0655
	12	372		0.0261	0.0156	59.9	0.00686	0.0402
	14	374		0.0104	0.00290	27.8	0.00648	0.0133
	17	377		NC	NC	NC	0.00615	0.0144
	20	380		NC	NC	NC	0.0078	0.078
	24	384		NC	NC	NC	0.00506	0.0166
	30	390		NC	NC	NC	0.0426	0.0426
	36	396		NC	NC	NC	0.0335	0.0335
	42	402		NC	NC	NC	0.0135	0.0135
	48	408		NC	NC	NC	0.0283	0.0283
	60	420		NC	NC	NC	0.0192	0.0192
	72	432		NC	NC	NC	0.0184	0.0184

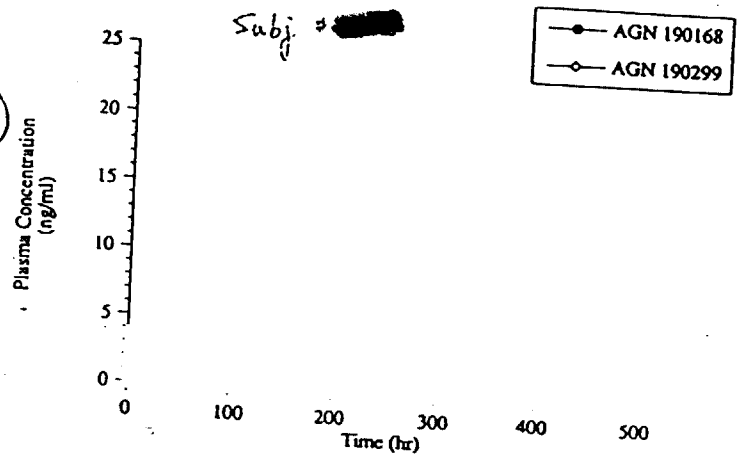
Appendix 9.3.4 Listing of Plasma Concentrations (ng/mL) versus Time of AGN 190299 by Subject, with Summary Statistics

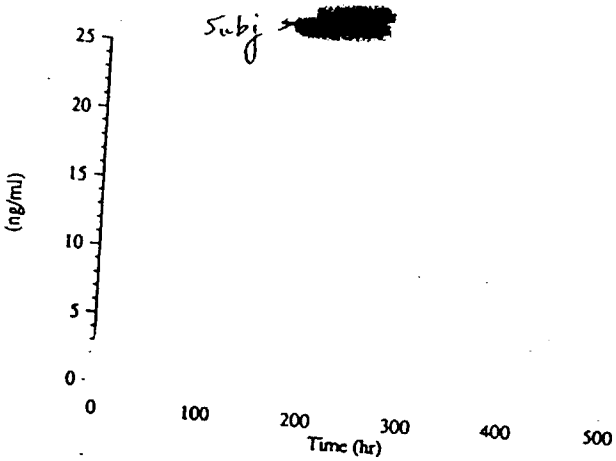
Dose No.	Time Since Previous Dose (hr)	Cumulative Time Since Start (hr)	Subject No.	Mean	S.D.	CV%	Minimum	Maximum
1	0	0		NC	NC	NC	NC	NC
	3	3		0.249	0.400	161	0.0355	0.961
	6	6		0.763	0.718	94.1	0.121	1.744
	9	9		1.01	0.931	91.9	0.134	2.308
	12	12		0.958	0.844	88.1	0.138	2.152
	14	14		0.823	0.745	90.6	0.127	1.922
	17	17		0.674	0.612	90.8	0.105	1.613
	20	20		0.432	0.398	92.2	0.0798	1.076
	24	24		0.347	0.307	88.5	0.0678	0.842
	30	30		0.218	0.187	85.7	0.0542	0.522
	36	36		0.184	0.163	88.5	0.0466	0.455
	42	42		0.143	0.136	95.5	0.0329	0.377
	48	48		0.0959	0.0796	83.0	0.0286	0.229
	60	60		0.0685	0.0567	82.8	0.0217	0.166
	72	72		0.0449	0.0434	96.7	0.0128	0.121
7	24	192		1.12	0.683	61.2	0.256	2.046
8	24	216		1.15	0.875	76.4	0.267	2.582
	3	219		3.90	3.43	87.9	0.656	9.04
	6	222		9.52	7.49	78.6	2.158	20.738
	9	225		5.81	4.30	74.1	1.406	12.64
	12	228		3.74	1.99	53.2	1.03	6.465
	14	230		2.67	1.27	47.6	0.957	4.514
	17	233		2.12	1.14	53.6	0.607	3.684
	20	236		1.54	0.785	51.1	0.425	2.538
	24	240		1.26	0.911	72.1	0.336	2.743
12	24	312		1.23	0.599	48.7	0.338	1.865
13	24	336		1.11	0.867	77.8	0.229	2.35
14	24	360		1.22	0.671	54.9	0.318	1.956
	3	363		5.89	4.76	80.7	1.583	13.265
	6	366		11.1	7.76	70.2	2.911	22.141
	9	369		6.89	3.88	56.3	1.815	11.979
	12	372		4.10	1.89	46.1	1.217	6.272
	14	374		2.92	1.16	40.0	0.983	3.837
	17	377		2.16	0.886	40.9	0.632	2.857
	20	380		1.56	0.684	43.7	0.442	2.15
	24	384		1.25	0.658	52.7	0.344	2.089
	30	390		0.777	0.342	44.1	0.302	1.168
	36	396		0.584	0.274	47.0	0.192	0.881
	42	402		0.429	0.243	56.7	0.135	0.74
	48	408		0.324	0.185	57.2	0.105	0.587
	60	420		0.231	0.137	59.6	0.0714	0.394
	72	432		0.133	0.0819	61.6	0.0417	0.233

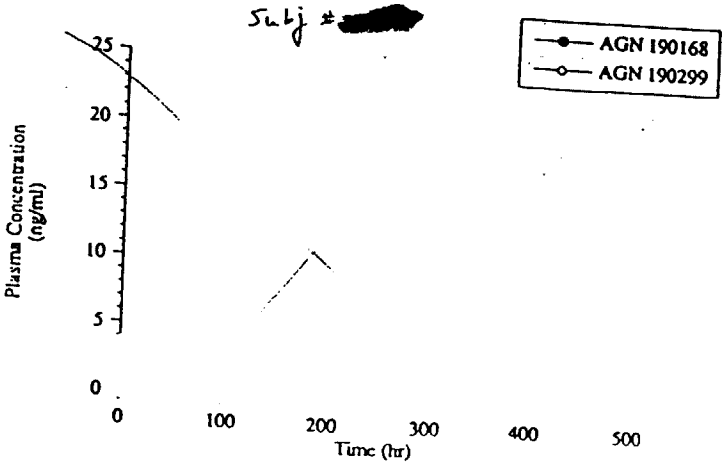
BLQ = Below limit of quantitation (0.05 ng/mL)


Subj #
AGN 190168
AGN 190299
Plasma Concentration (ng/ml)
25
20
15
10
5
0
0
100
200
300
400
500
Time (hr)


Subj #
(ng/ml)
25
20
15
10
5
0
0
100
200
300
400
500
Time (hr)


Subj #
AGN 190168
AGN 190299
Plasma Concentration (ng/ml)
25
20
15
10
5
0
0
100
200
300
400
500
Time (hr)


Subj #
(ng/ml)
25
20
15
10
5
0
0
100
200
300
400
500
Time (hr)


Subj #
AGN 190168
AGN 190299
Plasma Concentration (ng/ml)
25
20
15
10
5
0
0
100
200
300
400
500
Time (hr)

APPENDIX II. THERAPEUTIC DRUG LEVEL MONITORING:

1) Study R168-112-8606 (Vol. 1.69)

A one month comparison of the safety and tolerability of AGN 190168 0.1% and 0.05% gels once daily in volunteers with mild to moderate plaque psoriasis: A pilot study.

INVESTIGATOR AND LOCATION:

FORMULATION: Exact formulation, but slightly different manufacturing procedures (non-aq. to aq. phase addition).

STUDY DESIGN:
This was a double-blind, randomized study. Male and female subjects (n=15) with mild to moderate plaque psoriasis covering 1-15% of their body surface area were treated once daily in the evening for 28 days. Blood samples were collected after two and four weeks of treatment and 2-4 weeks post treatment.

ASSAY:

RESULTS:
After one month of treatment, no tazarotene was detected in any sample. Plasma metabolite concentrations were detected in 9 out of 15 patients after topical applications of % gel with the highest concentration being ng/mL. Washout period of 14-28 days were sufficient to achieve non-detectable metabolite concentrations.

2) Study R168-120-8606:

Safety, efficacy and duration of therapeutic effect of once-daily AGN 190168 0.1% gel or 0.05% gel versus vehicle gel in stable plaque psoriasis (Volume 1.69)

INVESTIGATOR AND LOCATION:
This study included 9 sites but only three sites were selected for plasma concentration monitoring.

FORMULATION: Exact formulation, but slightly different manufacturing procedures (non-aq. to aq. phase addition).

STUDY DESIGN:
This study was a double-blind, randomized, three-armed, parallel-group comparison study

with patients assigned to 0.1%, 0.05% or vehicle gel. Only patients with psoriasis not to exceed 20% of body surface area were accepted. Each of the three selected sites enrolled 36 patients. The gel or vehicle was applied to affected areas once daily in the evening for 12 weeks. Plasma concentrations were determined at week 0 (pre-dose), and 4, 8 and 12 weeks after treatment. The time of dose application prior to blood collection and time of blood collection were noted. The maximal daily dose was μg tazarotene/Kg based on a maximal dose of g of % gel and a body weight of Kg.

ASSAY:

RESULTS:

Of the patients selected for plasma concentration monitoring, 72 were drug-treated patients. Out of this pool, 34 patients (18 on 0.05% gel and 16 on 1.0% gel) had detectable plasma metabolite concentrations ranging ng/mL. Six patients had plasma metabolite concentrations greater than ng/mL with the highest value being ng/mL. (In a PK study with a dose of mg tazarotene/Kg in normal subjects, the highest plasma concentration found was ng/mL.)

There was no correlation between sampling time and plasma concentrations. Nor was there a correlation between baseline body surface area of treatment and plasma concentrations for the 0.05% gel or 0.1% gel treated group.

Only 2 patients had detectable tazarotene plasma concentrations. The highest concentration ng/mL) was observed with a patient having affected skin over 18% of her body surface area. This patient also had the highest plasma metabolite concentration ng/mL).

Of approximately 150 plasma samples where no drug or metabolite were anticipated, no detectable concentration of parent or metabolite was observed. However, one patient in the vehicle group had plasma concentration of tazarotene and metabolite at ng/mL, respectively at week 4. A sample withdrawn from one patient 13 days after last dose was analyzed to have plasma tazarotene concentration of ng/mL and undetectable metabolite concentration. The sponsor attributed these cases to contamination.

Comment:

Several possible factors can result in high plasma concentrations, e.g., skin permeability (disease state or nature of skin), actual dose used and exposure time to the applied dose.

3) **Study R168-121-8606:**

Safety and efficacy of once-daily AGN 190168 0.1% gel or 0.05% gel versus vehicle gel in

stable plaque psoriasis (Volume 1.71)

INVESTIGATOR AND LOCATION:
This study included 10 sites but only three sites were selected for plasma concentration monitoring:

FORMULATION: Exactly the same formulation and manufacturing procedures.

STUDY DESIGN:
This study was a double-blind, randomized, three-armed, parallel-group comparison study with patients assigned to 0.1%, 0.05% or vehicle gel. Male and female patients 12 years of age or older with stable psoriasis not to exceed 20% of body surface area were accepted. Each of the three selected sites enrolled 36 patients. The gel or vehicle was applied to affected areas once daily in the evening for 12 weeks. Plasma concentrations were determined at week 0 (pre-dose), and 4, 8 and 12 weeks after treatment. The time of dose application prior to blood collection and time of blood collection were noted. The maximal daily dose was 97 μg tazarotene/Kg based on a maximal dose of 6.8 g of 0.1% gel and a body weight of 70 Kg.

ASSAY:

RESULTS:
After 12 weeks of topical treatment with either the 0.1% or 0.05% tazarotene gel applied on up to 20% of the total body surface area once daily, low plasma tazarotene concentrations were detected (up to ng/mL) in 2 of the 70 drug-treated patients. One of the patient was treated over 4% of his body surface area and the other over 20% of his body surface area with the 0.1% gel.

Out of the 70 drug treated patients, 43 (21 on 0.05% gel and 22 on 1.0% gel) had detectable plasma concentrations of the free acid metabolite ng/mL). Nine patients had concentrations greater than ng/mL.

Of approximately 150 plasma samples where no drug or metabolite were anticipated, no detectable concentration of parent or metabolite was observed. However, it was determined after unblinding of the treatment code, that two patients in the vehicle control group had measurable plasma concentrations of tazarotene or metabolite. The sponsor attributed this to contamination and implemented procedures to improve quality of study and sample handling.

4) **Study R168-125-8606:** (Volume 1.71)

Safety, efficacy and duration of therapeutic effect of AGN 190168 0.1% gel or 0.05% gel applied once daily versus Lidex (fluocinonide) 0.05% cream applied twice daily in stable

plaque psoriasis

INVESTIGATOR AND LOCATION:
This study included 10 sites but only three sites were selected for plasma concentration monitoring:

FORMULATION: Exactly the same formulation and manufacturing procedures.

STUDY DESIGN:
This study was a single-blind, randomized, three-armed, parallel-group comparison study with patients assigned to 0.1% or 0.05% tazarotene gel or Lidex 0.05% cream. Male and female patients 12 years of age or older with stable psoriasis not to exceed 20% of body surface area were accepted. The gel was applied to affected areas once daily in the evening and the cream twice daily, once in the morning and once in the evening, for 12 weeks. Plasma concentrations were determined at week 0 (pre-dose), and 4, 8 and 12 weeks after treatment. The maximal daily dose was 97 μg tazarotene/Kg based on a maximal dose of 6.8 g of 0.1% gel and a body weight of 70 Kg.

ASSAY:

RESULTS:
Of the 72 patients treated with the subject drug, 50 patients (23 on 0.05% gel and 27 on 0.1% gel) had detectable plasma metabolite concentrations ranging from ng/mL with 4 patients having concentrations greater than 1 ng/mL. Only one patient had detectable plasma tazarotene concentration. This patient was treated over 5% of his body surface area. Of approximately 150 plasma samples where no drug or metabolite were anticipated, no detectable concentration of parent or metabolite was observed. However, it was determined after unbinding of the treatment code, that two patients in the vehicle control group had measurable plasma concentrations of tazarotene or metabolite. The sponsor attributed this to contamination and implemented procedures to improve quality of study and sample handling.

5) **Study R168-126-8606:** (Volume 1.71)

Safety, efficacy and duration of therapeutic effect of AGN 190168 0.1% gel or 0.05% gel applied once daily versus Lidex (fluocinonide) 0.05% cream applied twice daily in stable plaque psoriasis

INVESTIGATOR AND LOCATION:
This study included 9 sites but only three sites were selected for plasma concentration monitoring.

FORMULATION: Exactly the same formulation and manufacturing procedures.

STUDY DESIGN:
This study was a single-blind, randomized, three-armed, parallel-group comparison study with patients assigned to 0.1% or 0.05% tazarotene gel or Lidex 0.05% cream. Male and female patients 12 years of age or older with stable psoriasis not to exceed 20% of body surface area were accepted. The gel was applied to affected areas once daily in the evening and the cream twice daily, once in the morning and once in the evening, for 12 weeks. Plasma concentrations were determined at week 0 (pre-dose), and 4, 8 and 12 weeks after treatment. The maximal daily dose was μg tazarotene/Kg based on a maximal dose of 6.8 g of 0.1% gel and a body weight of 70 Kg.

ASSAY:

RESULTS:
Of the 69 patients treated with the subject drug, 47 patients (23 on 0.05% gel and 24 on 0.1% gel) had detectable plasma metabolite concentrations ranging from ng/mL with 6 patients having concentrations greater than 1 ng/mL.

Only one patient had detectable plasma tazarotene concentration (ng/mL). This patient was treated over 3% of his body surface area.

6) **Study R168-145-8606:**

Safety, efficacy and duration of therapeutic effect of once- daily AGN 190168 0.1% gel or once- daily AGN 190168 0.05% gel versus twice-daily calcipotriol 0.005% ointment in plaque psoriasis: An investigator masked study (Study date: 9/93-6/94; Volume 1.72)

INVESTIGATOR AND LOCATION:
This study involves 15 investigators in 15 non-U.S. sites.

OBJECTIVES:
This study investigated the safety, efficacy and duration of therapeutic effect of two concentrations (0.1% and 0.05%) of tazarotene gel versus calcipotriol 0.005% ointment for the treatment of stable plaque psoriasis. The plasma tazarotene and the free acid metabolite were determined in 191 patients.

FORMULATION: Exact formulation and manufacturing procedures.

STUDY DESIGN:
This study was a single-blind, randomized, three-armed, parallel-group comparison study with patients assigned to 0.1% or 0.05% tazarotene gel or calcipotriol 0.005% ointment. Male and female patients 12 years of age or older with stable psoriasis not to exceed 20% of body surface area were accepted. The gel was applied to affected areas once daily in the evening and the ointment twice daily, once in the morning and once in the evening, for 12 weeks. Plasma concentrations were determined at week 0 (pre-dose), and 1, 4, 8, 12, 16, 20 and 24 weeks after treatment. The maximal daily dose was μg tazarotene/Kg based on a maximal dose of g of % gel and a body weight of Kg.

ASSAY:

RESULTS:
A total of 191 patients received the subject drug and had their plasma assayed. Tazarotene was not detected in any sample, while the metabolite was detected in 97 patients (48 patients on 0.01% gel and 49 on the 0.05% gel). Note that the LOQ for the assay was ng/mL. Twenty-three patients had plasma metabolite concentrations greater than ng/mL, including one patient at ag/mL. No patient had detectable plasma metabolite concentration during the follow-up phase (weeks 16-24). Plasma metabolite concentrations were detected in 2 pre-dose samples and it was attributed to sample mislabeling.

7) **Study R168-220-7997** (Vol. 1.69)

Safety and efficacy of AGN190168 in the treatment of acne vulgaris: AGN190168 (0.1% and 0.05%) gels versus vehicle gel

OBJECTIVES:
To investigate the safety and efficacy of two concentrations (0.1% and 0.05%) of tazarotene gel formulations versus a vehicle gel for the treatment of acne vulgaris.

STUDY DESIGN:
This is a double-blind, randomized, three-arm, parallel-group study. Up to 450 subjects with mild to moderate facial acne vulgaris were enrolled into the study. Daily dose was estimated to be 10 and 5 μg tazarotene/Kg (or 500 mg of gel/50 Kg) for the 0.1% and 0.05% gels, respectively. The assigned formulation was applied once daily for 12 weeks. About the first third of patients enrolled at each of the 2 sites were selected for plasma drug monitoring. Blood samples were drawn at 0-week, and weeks 8 and 12 for determination of plasma concentrations.

ASSAY:

RESULTS:
A total of 112 subjects had blood samples drawn, and samples from 34 subjects were selected for analysis. Out of the selected 34 subjects, 22 (11M/11F) received the subject drug (12 received 0.05% gel and 10 received 0.1% gel). Most samples (45 out of 54) showed concentrations below the limit of quantitation. Of all the samples analyzed, the concentrations ranged from ng/mL for tazarotene and ng/mL for the metabolite.

Three problematic sample results occurred where drug or metabolite were not anticipated but were detected. The sponsor attributed this to contamination.

8) **Study R168-221-8606** (Vol. 1.71)

Safety and efficacy of AGN190168 in the treatment of acne vulgaris: AGN190168 0.1% and 0.05% gels versus vehicle gel

OBJECTIVES:
To investigate the safety and efficacy of two concentrations (0.1% and 0.05%) of tazarotene gel formulations versus a vehicle gel for the treatment of acne vulgaris.

STUDY DESIGN:
This is a multi-center (9 sites), double-blind, randomized, three-arm, parallel-group study. A total of 446 subjects, 12 years of age or older, with facial acne vulgaris were enrolled into the study. The assigned formulation was applied once daily for 12 weeks. Daily dose was estimated to be 10 and 5 μg tazarotene/Kg (or 500 mg of gel/50 Kg) for the 0.1% and 0.05% gels, respectively. Patients enrolled at each of the 2 specified sites were selected for plasma drug monitoring. Blood samples were drawn at 0-week, and weeks 8 and 12 for determination of plasma concentrations.

ASSAY:

RESULTS:
Of the 70 drug-treated patients, only one patient had detectable plasma tazarotene concentration ng/mL) and 8 patients (3 on 0.05% gel and 5 on 0.1% gel) had detectable plasma metabolite concentrations ng/mL).

One problematic sample results occurred where plasma tazarotene concentration was detected in a patient on vehicle. The sponsor attributed this to contamination.

Comment: Problematic sample results could be due to sample mix-up or contamination or problem with assay specificity.

9) **Study R168-210-8225** (Vol. 1.72)

Safety and efficacy of AGN190168 in the treatment of acne vulgaris: AGN190168 0.05% and 0.1% gels versus vehicle gel

OBJECTIVES:
To investigate the safety and efficacy of two concentrations (0.1% and 0.05%) of tazarotene gel formulations versus a vehicle gel for the treatment of acne vulgaris.

COMMENT:
A brief summary of the study was provided. This was a double-blind, randomized, three-arm, parallel-group study. The applied doses were 3.57 and 0.71 μg/Kg/day and blood samples were drawn 15-20 hours post last dose. Plasma samples were analyzed by a method with a ng/mL. Samples from 20 subjects (19M/1F; 5 on vehicle, 5 on 0.05% gel and 10 on 0.1% gel) registered no detectable concentrations of tazarotene or metabolite (M1).

10) **Study R168-128-8606:**

Safety and Efficacy of Once-Daily AGN190168 0.1% Gel and AGN190168 0.05% Gel in the Long-Term (up to one year) Treatment of Stable Plaque Psoriasis (Vol. 2.1, 2.20)

FORMULATION: 0.1% and 0.05% gel

STUDY DESIGN:
This study was a double-blind, randomized, parallel-group clinical trial in 12 U.S. centers with patients assigned to 0.1% or 0.05% tazarotene gel. Male and female patients 18 years of age or older with stable psoriasis not to exceed 20% of body surface area were accepted. The gel was applied to the affected areas once daily in the evening for up to one year. Plasma concentrations of tazarotene and its active metabolite were determined at pre-dose, and 3, 6, 9 and 12 months after treatment.

ASSAY:

RESULTS:

A total of 243 patients (154 males and 89 females) entered the study and only 101 patients completed the study. Out of the 142 patients who discontinued the study, 59 were due to adverse events, 34 due to lack of efficacy, 42 due to administrative reasons and 7 were disqualified.

Tazarotene:
Plasma tazarotene concentrations were detected in 3 patients and all were below 1 ng/mL with the higest concentration being ng/mL.

Active metabolite:
Plasma concentrations of the active metabolite were detected in 31 patients, 18 patients treated with 0.1% gel and 13 treated with 0.05% gel. Four patients had concentrations greater then ng/mL with 2 patients in each treatment group, and the highest concentration was ng/mL.

APPENDIX III. IN VITRO STUDIES

A. In Vitro Drug Penetration, Distribution and Metabolism in Skin:

1) IN VITRO COMPARISON OF TWO GEL FORMULATIONS (Vol. 1.69)

BACKGROUND:
Two formulations used in the PK studies differ in neutralizing agent. The to-be-marketed formulation (#8606X for 0.1% gel and #8607X-A for 0.05% gel) contains % tromethamine while the formulation developed earlier (#7997X for 0.1% gel and #8225X for 0.05% gel) contains % This study compared the skin penetration and drug distribution of the two formulations. The 0.1% gel formulations were used in the study.

EXPERIMEATAL:
Human cadaver skin was cut to a thickness of approximately 250 μm and mounted onto Franz diffusion cells. Each formulation was applied at a dose of 10 mg/cm^2. The receptor solution contained phosphate-buffered saline (pH 7.4) and 0.5% Volpo 20 and was maintained at 37°C. At the end of the experiment (48 hours), the skin was washed, removed from the chamber and separated into epidermis and dermis. Skin tissues were digested and all samples were measured for radioactivity by

RESULTS:
Total recovery of radioactivity from surface washes and the skin tissues was approximately 90% for both formulations. Drug distribution in skin layers and quantity of drug present in the receptor fluid were similar for the two formulations. At 48 hour post-dose, the drug in the epidermis and dermis was about 2.5% and 2.0%, respectively. Approximately 1.0% of the dose was in the receptor solution.

Comment: The text indicated that data presented were for the 48 hour period while the table indicated a 24 hour period. One of them is in error.

***In vitro* Permeation of ^{14}C-Tazarotene Through Human Skin When Topically Applied in Two Gel Formulations (recovery of radioactivity over a 24 hour period as % of dose applied)**

Component	Formulation Number	
	8606X-14C	7997X-14C
Unabsorbed	85.3 ± 7.8	85.4 ± 6.1
Epidermis	2.74 ± 1.10	2.45 ± 1.43
Dermis	1.48 ± 0.88	2.06 ± 1.98
Receptor reservoir	0.94 ± 0.60	1.04 ± 0.53
Total recovery	90.4 ± 7.6	90.1 ± 4.8

Values are mean ± SD, n = 5.

2) IN VITRO SKIN PERMEATION - DISTRIBUTION

EXPERIMENTAL:

Full-thickness skin was used to evaluate the in vitro penetration of tazarotene. Human cadaver skin and fresh human skin were tested along with fresh fuzzy rat skin. ^{14}C-tazarotene gel containing 0.01% tazarotene was topically applied to the skin surface. The receptor chamber contained phosphate buffered saline (pH 7.4) with 20% PEG-300 at 32°C. At 24 hour post-dose, the gel was removed from the skin surface and the stratum corneum removed by tape-stripping. The radioactivity in the stratum corneum and residual skin (viable epidermis-dermis) was extracted. All samples were measured for radioactivity content by

RESULTS:

At 24 hours post-dose, the % dose present in stratum corneum, viable epidermis-dermis and receptor fluid are given in the table below.

Comment: The formulation was not given. The experimental conditions for this study were different from those for the previous study making comparison difficult.

Radioactivity Distribution in Skin Layers and in Diffusate as the % Dose Applied After 24-Hour Permeation *In vitro*

	Fresh Fuzzy Rat Skin	Human Cadaver Skin	Fresh Human Skin
Stratum Corneum	5.63 (3.77)	4.52 (2.18)	3.63 (1.29)
Residual Skin	9.04 (7.52)	2.17 (1.34)	3.52 (2.74)
Receptor Chamber Fluid	0.31 (0.29)	0.09 (0.02)	0.52 (0.78)
n	4	8	5

Values are mean (SD).

3) DRUG METABOLISM IN SKIN

EXPERIMENTAL:

Human cadaver skin and fresh human skin were tested along with fresh fuzzy rat skin. ^{14}C-tazarotene gel (25 mg) containing 0.01% tazarotene was topically applied to the skin surface for 24 hours. The nature of the radioactivity in the stratum corneum and residual skin (viable epidermis-dermis) was analyzed by

RESULTS:

Disposition of ^{14}C-Tazarotene as % Total Radioactivity in Each Skin Layer *In vitro*

	Fresh Fuzzy Rat Skin	Human Cadaver Skin	Fresh Human Skin
Stratum Corneum:			
Tazarotene	85.2	80.4	82.8
AGN 190299	14.8	19.6	17.2
Viable Epidermis/ Dermis:			
Tazarotene	57.8	64.2	67.7
AGN 190299	47.2	35.8	32.3
Receptor Fluid:			
Tazarotene	3.44	NA	46.0
AGN 190299	96.6	NA	54.0

B. Metabolism of Tazarotene:

1) IN VITRO METABOLISM OF AGN 190168 IN THE BLOOD OF MALE JAPANESE-AMERICAN AND CAUCASIAN (Vol. 1.69)

BACKGROUND:

In two U.S. human PK studies in healthy Caucasian volunteers, the metabolite but not the parent compound was detected in blood samples after topical administration of a tazarotene gel. Similar studies conducted in Japanese volunteers showed that the parent compound was detectable in blood samples. Therefore, this study was conducted to examine and compare the metabolism of tazarotene and the activities of total esterases, aromatic esterase, cholinesterase and carboxyesterase in the blood of Japanese-American and Caucasian subjects.

OBJECTIVE:

To compare the hydrolysis of tazarotene by blood esterase between Japanese-American and Caucasian subjects.

EXPERIMENTAL:

Human blood (25-30 mL per subject) was obtained from 10 healthy Japanese-American and 10 healthy Caucasian volunteers. Stock solutions (500 μg/mL) and Standards (62.5, 125, 250, 500 and 1000 ng/mL) of tazarotene and the free acid metabolite were prepared in % acetonitrile.

a. Metabolism of Tazarotene in Human Blood:

Tazarotene μg) was added to mL of each volunteer's blood, vortexed, and incubated at 37°C. An aliquot (0.5 mL) was removed from each vial at 1, 2, 3, 4 and 6 hours and placed into a test tube containing a 1:1 acetonitrile:1-butanol extraction solution. AGN 190252 was used as the internal standard. The tube was vortexed, centrifuged and the supernatant layer was removed and evaporated to dryness under nitrogen gas. Each sample was reconstituted in mobile phase and analyzed for tazarotene and the free acid metabolite using equipped with detector.

b. Total Esterases:

To determine blood or plasma total esterase activities, α-naphyl acetate (3 ml of 60 μM solution in 0.1M Tris buffer at pH 7.4) was added as substrate to hemolysate or plasma μl), and measurement was made spectrofluorometrically based on the formation of α-naphthol (excitation λ: 317 nm, detection λ: 470 nm) for 5 minutes. The concentrations of standard α-naphthol solutions ranged from nmol/ml.

c. Aromatic Esterase:

To determine plasma aromatic esterase activity, p-nitrophenyl acetate (975 μl of a 4 mM solution) was added as substrate to plasma (25μl), and measurement was made spectrophotometrically based on the formation of p-nitrophenol at 385 nm for 2 minutes. The change in absorbance is not linear over the 2 minutes and the initial slope was used to calculate

the enzyme activity. The concentrations of standard p-nitrophenol solutions ranged from nmol/ml.

d. Cholinesterase:

was used to determine blood or plasma cholinesterase activity. Cholinesterase hydrolyzes propionylthiocholine to form thiocholine which reacts with 5,5'-dithiobis-2-nitro-benzoic acid to yield the yellow 5-thio-2-nitrobenzoate with an absorbance maximum at 405 nm. Therefore, measurements were made at 405 nm.

e. Carboxyesterase:

To determine blood or plasma carboxyesterase activities, 4-methylumbelliferyl acetate (μl of mM solution mixed with ml of mM acetate buffer at pH 5.5) was added as substrate to hemolysate or plasma (μl), and measurement was made spectrofluorometrically based on the formation of 4-methylumbelliferone (excitation λ: 320 nm, detection λ: 445 nm) for 5 minutes. The concentrations of standard 4-methylumbelliferone solutions ranged from pmol/ml.

DATA ANALYSIS:

The differences between the two groups were compared by Student's two-sided t-test. The level of significance, α, was set at 0.05.

RESULTS:

The concentrations recovered as tazarotene and the free acid metabolite remained constant over the 6 hour incubation period, indicating that tazarotene was mainly converted to the free acid for both groups. A semilogarithmic plots of blood concentration of tazarotene versus time yielded straight lines indicating a first order disappearance. The rate constants for the tazarotene disappearance from blood of Japanese American and Caucasian were 0.197 ± 0.092 hr^{-1} (or $t_{1/2} = 3.73 \pm 0.33$ hours) and 0.202 ± 0.022 hr^{-1} (or $t_{1/2} = 4.25 \pm 0.61$ hours), respectively. The formation rate of the metabolite varied with time and the initial rates were 1140 ± 120 ng/hr and 1120 ± 90 ng/hr, respectively. There was no statistically significant difference in these parameters between the two groups.

Investigation of the esterase activities showed that there was no difference in blood or plasma activities of aromatic esterase (plasma only), carboxyesterase, cholinesterase and total esterases in both groups.

Comment:

Hydrolysis can occur in solution even without esterases. Was the contribution of chemical degradation ruled out in the determination of metabolic deesterification?

Table L- Kinetic parameters of AGN 190168 in the blood of Caucasian and Japanese-American subjects *in vitro*. Values are mean ± S.E.M., n= 10.

	AGN 190168 k (hr^{-1})[a]	AGN 190168 $t_{1/2}$ (hr)[b]	Initial rate of AGN 190299 formation (ng/hr)
Caucasians	0.197 ± 0.029	4.25 ± 0.61	1140 ± 120
Japanese-Americans	0.202 ± 0.022	3.73 ± 0.33	1120 ± 90

[a] First order rate constant for the disappearence AGN 190168 in blood.

[b] Half-life of AGN 190168 in the blood.

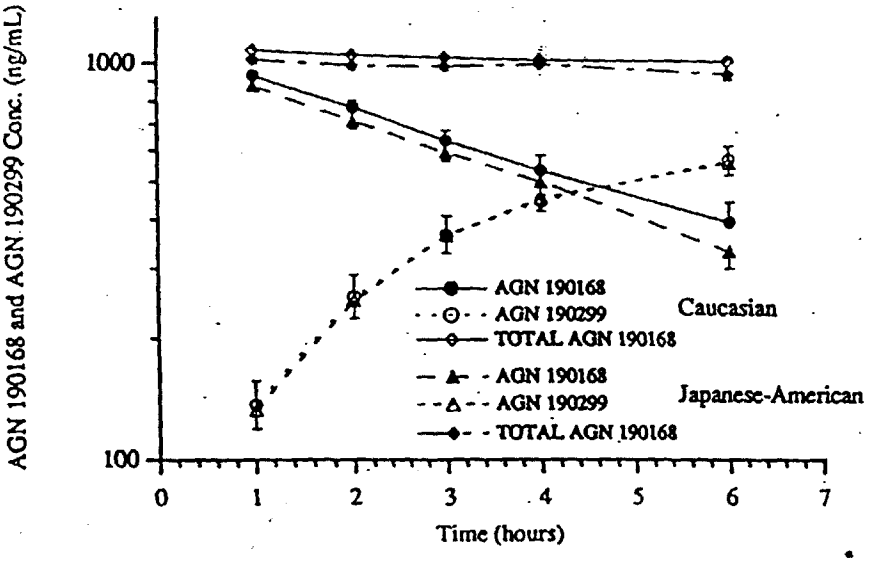


Figure 3. Disappearance of AGN 190168 and formation of AGN 190299 and total AGN 190168 in blood of Japanese-American and Caucasian male subjects (see data analysis section). Values are mean ± S.E.M., n = 10.

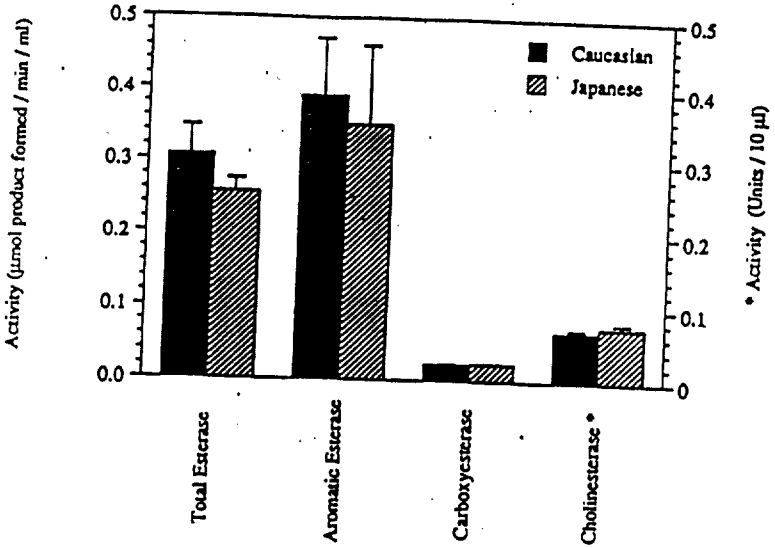


Figure 4. Activities of total esterase, aromatic esterase, carboxyesterase, and cholinesterase in the plasma of Japanese-American and Caucasian male subjects (measured using standard substrates of α-napthyl acetate, *p*-nitrophenyl acetate, 4-methylumbelliferyl acetate and propionylthiocholine, respectively). Values are mean ± S.E.M., n = 10.

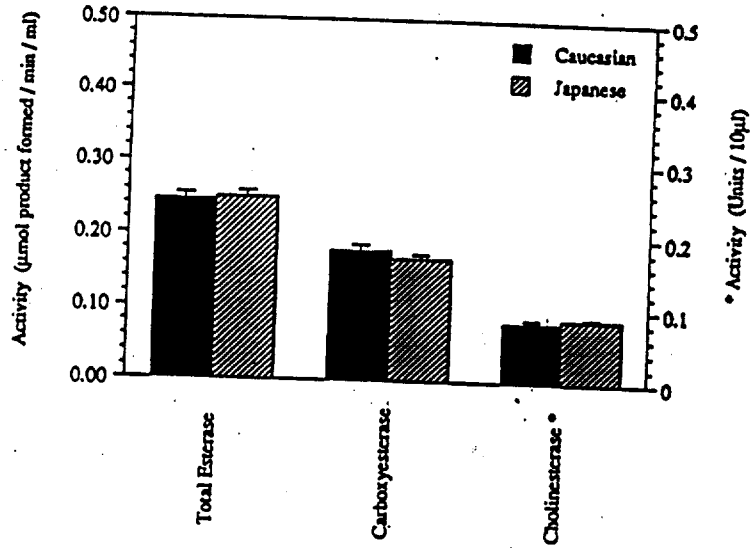


Figure 5. Activities of total esterase, carboxyesterase and cholinesterase in the blood of Japanese-American and Caucasian subjects (measured using standard substrates of α-napthyl acetate, 4-methylumbelliferyl acetate and propionylthiocholine, respectively). Values are mean ± S.E.M., n = 10.

2) THE EFFECT OF ESTERASE INHIBITORS ON THE IN VITRO METABOLISM OF AGN 190168 IN HUMAN BLOOD (Vol. 1.69)

OBJECTIVE:

This study was conducted to examine the esterase(s) responsible for hydrolyzing tazarotene in human blood in vitro.

EXPERIMENTAL:

Blood was collected from four healthy male human subjects. Five ml of each volunteer's blood was preincubated for 20 min at 37°C with four specific esterase inhibitors: physostigmine (0.1 mM) as cholinesterase inhibitor, bis-p-nitrophenyl phosphate (0.1 mM) as carboxyesterase inhibitor, EDTA (1.0 mM) as arylesterase inhibitor and paraoxon (0.1 mM) as an inhibitor for all serine type esterases including cholinesterase and carboxyesterase. Tazarotene μg) was then added to the above mixture and incubated at 37°C for 6 hours. Samples were taken immediately and 6 hours after incubation. The inhibition of enzyme activity was assessed by monitoring the disappearance of tazarotene and the formation of the free acid metabolite with a reversed phase HPLC using UV detection.

RESULTS:

Approximately 75% of tazarotene was hydrolyzed to the free acid metabolite within 6 hours. Physostigmine, bis-p-nitrophenyl phosphate and EDTA produced no statistically significant effect on the hydrolysis of tazarotene in the blood. Paraoxon, statistically significantly decreased the metabolic hydrolysis of tazarotene to the free acid by 95%. These results indicates that paraoxon-inhibitable esterases are involved in metabolizing tazarotene in human blood in vitro.

3) IDENTIFICATION OF A POLAR HUMAN FECAL METABOLITE OF AGN 190168 (Vol. 1.72, p. 42)

OBJECTIVE:

At least one polar metabolite of tazarotene has been detected in urine, feces and animal tissues, and comprises as much as 60% of fecal radioactivity after topical or IV administration of ^{14}C-tazarotene to rats or humans. The purpose of this study was to identify this metabolite.

EXPERIMENTAL:

RESULTS:

The metabolite has a molecular weight of 338 and a neutral loss of 44 mass units. It was identified as an oxygenated derivative of the free acid metabolite. However, the position of oxygen could not be pinpointed with the technique used. It was suspected that the compound was an N-oxide.

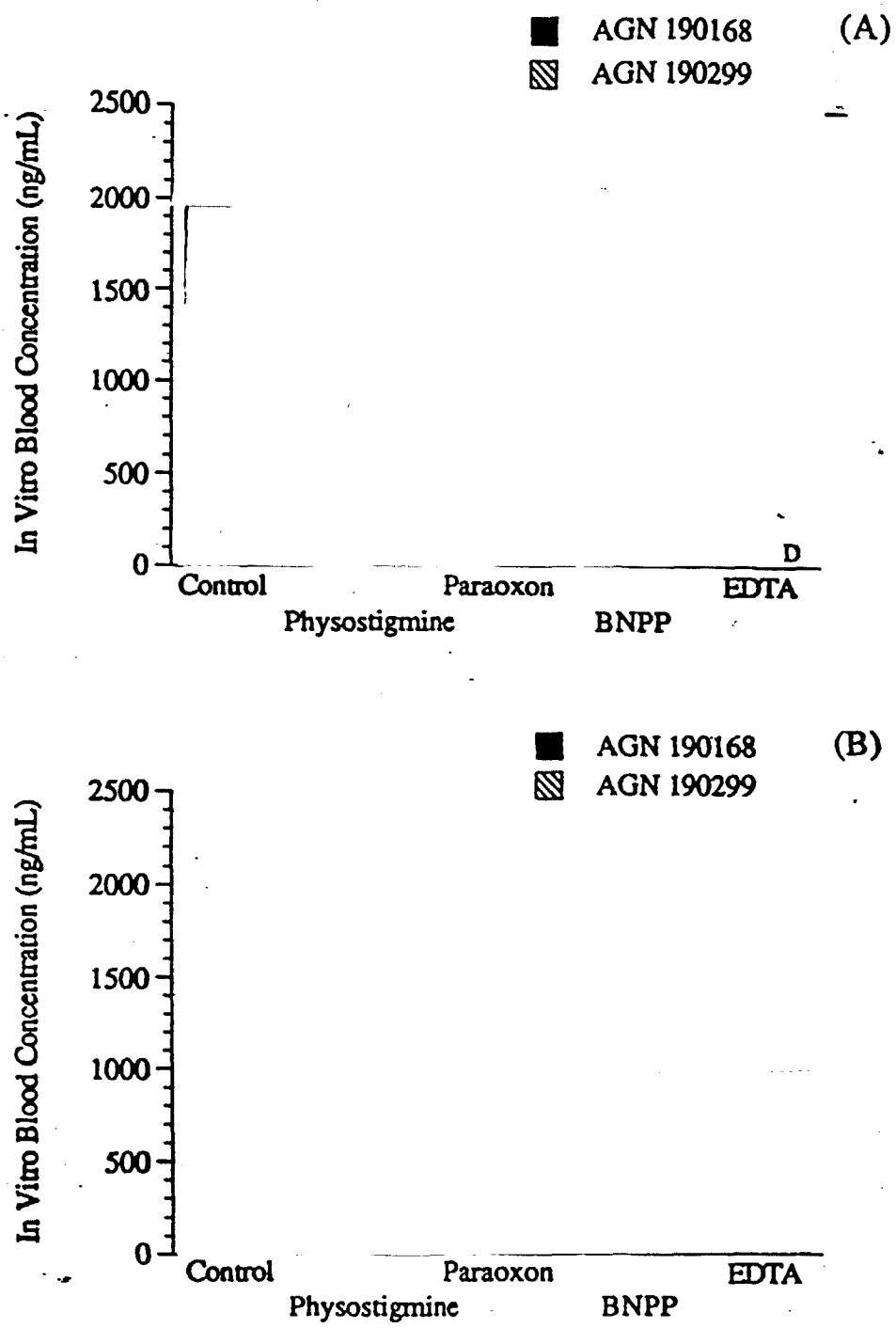


Figure 1. Effect of various esterase inhibitors on the metabolism of AGN 190168 in human blood *in vitro* after 0 and 6 hours of incubation at 37°C (panels A and B respectively). Values are mean ± SEM, n = 4. Inhibitor concentrations were 0.1 mM with the exception of EDTA which was 1.0 mM. ND = not detected; BNPP = bis-*p*-nitrophenyl phosphate; EDTA = ethylenediaminetetraacetic acid.

APPENDIX IV: ANALYTICAL METHODS:

A) PLASMA SAMPLES:

The stability of tazarotene and the free acid metabolite in human plasma was tested at two concentrations (20 and 300 ng/mL) and at two storage temperatures (RT and -20°C) using a method. Both tazarotene and the metabolite were stable at room temperature and at -20°C for up to 24 hours and 16 months, respectively.

Quality control samples kept at RT for greater than 48 hours for tazarotene and 144 hours for the metabolite appeared to remain stable.

1) In early development of tazarotene, an method was used. Plasma samples were added an internal standard (AGN 190252) and double-extracted using acetonitrile:ethylacetate mixture followed by an acetonitrile:1-butanol mixture. The extract was evaporated to dryness, reconstituted with mobile phase and injected onto a reversed phase C_{18} column. (Vol. 1.72)

Linearity:	10-500 ng/mL (tazarotene),	20-500 (metabolite); r=0.999
Precision (%CV) at LOQ:	Tazarotene - 15% ,	Metabolite - 12%
Accuracy (%) at LOQ:	Tazarotene - 109%,	Metabolite - 108%
LOQ:	Tazarotene - 10 ng/mL,	Metabolite - 20 ng/mL

Specificity: No interfering peaks from blank plasma

2) a. Later, a method was used for analyzing tazarotene and the free acid metabolite in human plasma. The assay employed d_7-tazarotene and d_7-free acid as internal standards and involved the extraction with solid phase C_{18} columns and differential elution of the parent compound and metabolite. The eluates, methanolic aqueous solution for the metabolite and ethyl acetate for the parent, were evaporated to dryness. The metabolite sample was derivatized with pentafluorobenzyl bromide and evaporated to dryness. Samples were reconstituted with dimethylformamide and injected onto a system. The tazarotene ion was monitored at m/z 351 and the d_7-tazarotene ion at m/s 358. The derivatized metabolite ion was monitored at m/z 322 and its internal standard at m/z 329. The validation results are as follows:

Linearity:	0.05 - 5 ng/mL r=0.999	
Precision (%CV):		
Tazarotene:	1.4 - 5.2 (intraday);	2.6 - 12.0 (interday)
Metabolite:	2.4 - 9.5 (intraday)	3.5 - 14.0 (interday)
Accuracy (% deviation from actual concentration):		
Tazarotene:	0.1 - 6.8 (intraday);	3.0 - 28.0 (interday)
Metabolite:	2.0 -5.0 (intraday)	5.0 - 18.0 (interday)
LOQ:	ng/mL	

Specificity: No interfering peaks from blank plasma

b. For the Phase 1 trial conducted in Japan, whole blood samples were analyzed by a

modified method where 2 mL of blood samples were extracted with acetonitrile:1-butanol mixture before they were applied onto solid phase C_{18} columns. The validation results are given below (Vol. 1.72).

Linearity: 0.02 - 1 ng/mL r≥0.997
Precision (%CV):
Tazarotene: 7.2 - 9.6 (intraday); 3.4 - 9.4 (interday)
Metabolite: 12 - 14 (intraday) 4.1 - 22 (interday)
Accuracy (% deviation from actual concentration):
Tazarotene: 5.6 - 14 (intraday); 2.0 - 6.3 (interday)
Metabolite: 0.2 - 7.2 (intraday) 0.0 - 7.6 (interday)
LOQ: ng/mL
Specificity: No interfering peaks from blank plasma

c) An improved method was used for 2 PK studies (R168-155-8757). The validation results are as follows:

Linearity: 0.005 - 5 ng/mL r≥
Precision (%CV):
Tazarotene: (intraday); (interday)
Metabolite: (intraday) (interday)
Accuracy (% deviation from actual concentration):
Tazarotene: (intraday); (interday)
Metabolite: (intraday) (interday)
LOQ: ng/mL
Specificity:

3) method: This method with rapid throughput was used for analyzing the plasma drug concentrations in patients participated in later clinical efficacy trials. The method employed Plasma samples were slightly acidified and extracted with an ethyl acetate:hexane mixture. The organic phase was evaporated to dryness, reconstituted in mobile phase and injected onto a column followed by gradient elution. The ion fragmentation reactions monitored were: 352 to 324 for tazarotene, 359 to 331 for d_7-tazarotene, 322 to 278 for the free acid metabolite and 329 to 285 for d_7-free acid.

Linearity: 0.2 - 20 ng/mL
r≥0.996 (tazarotene); r=0.989-0.993 (metabolite)
Precision (%CV):
Tazarotene: 9.0 - 10 (intraday); 3.1 - 14 (interday)
Metabolite: 6.6 - 13 (intraday) 1.0 - 7.6 (interday)
Accuracy (% deviation from actual concentration):
Tazarotene: 1.7 - 8.0 (intraday); 0.3 - 7.0 (interday)
Metabolite: 3.0 - 10 (intraday) 1.0 - 14 (interday)

LOQ: ng/mL
Specificity: No interfering peaks from blank plasma

B) URINE SAMPLES: (Vol. 1.70)

1) assay method: The method is similar to used for analyzing plasma samples obtained from efficacy trials except that two additional metabolites were also determined. The ion fragmentation reactions monitored were: 352 to 324 for tazarotene, 359 to 331 for d_7-tazarotene, 324 to 294 for the free acid (AGN 190299, metabolite 1), 331 to 297 for d_7-free acid, 368→280 for AGN 190832 (metabolite 2) and 340→280 for AGN 190844 (metabolite 3).

Linearity: 1 - 100 ng/mL, $r \geq 0.989$ (1-50 ng/mL for metabolite 4)

Precision (%CV):

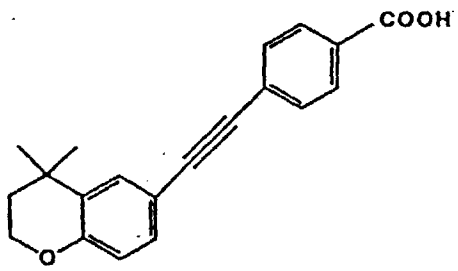
Tazarotene:	2.2 - 4.1 (intraday);	1.5 - 6.5 (interday)
Metabolite 1:	2.4 - 9.9 (intraday)	2.8 - 8.5 (interday)
Metabolite 2:	3.0 - 9.0	2.3 - 29
Metabolite 3:	7.2 - 14	0.4 - 11

Accuracy (%):

Tazarotene:	3.0 - 13 (intraday);	0.3 - 5.0 (interday)
Metabolite 1:	9.0 - 9.9 (intraday)	0.6 - 17 (interday)
Metabolite 2:	2.0 - 12	2.4 - 21
Metabolite 3:	1.0 - 12	2.0 - 14

LOQ: ng/mL
Specificity: No interfering peak found in the blank.

Comment:
The stability of tazarotene and metabolite in biological samples should be tested at the concentration range similar to that found in PK studies and clinical trials.



Chemical Structure of AGN 190252
(Internal standard)

OCT 31 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-600
PRODUCT: Tazarotene Gel, 0.05%, 0.1%
SPONSOR: Allergan
2525 Dupont Drive, P.O. Box 19534
Irvine, CA 92713-9534
TYPE OF SUBMISSION:
NDA Amendment

SUBMISSION DATES:
06/27/96, 07/30/96
09/18/96, 10/29/96

REVIEWER: Sue-Chih Lee, Ph.D.

I. BACKGROUND:

Tazarotene is intended for topical treatment of plaque psoriasis and acne vulgaris. It is an acetylenic retinoid and is converted to its active form, tazarotenic acid in biological systems by de-esterification. The sponsor was issued a non-approvable letter dated June 6, 1996 which listed all deficiencies. All comments which were not the basis of non-approval action were communicated to the sponsor via a fax transmission also dated June 6, 1996. Subsequently, the sponsor submitted amendments to address the issues cited in these communications.

II. SPONSOR'S RESPONSES TO COMMENTS:

DEFICIENCY #1.
The stability of tazarotene and metabolite in biological samples should be tested at the concentration range similar to that found in PK studies and clinical trials.

SPONSOR'S RESPONSE:
Tazarotene and its active metabolite at the concentration range of ng/mL were shown to be stable at -80°C up to 18 months and at -20°C for 8 months. These stability data are submitted. Later, the room temperature stability data for both tazarotene and its active metabolite (2-3 ng/mL) in blood and plasma samples stored at 21°C for up to 4 hours were provided. The sponsor stated in a subsequent telecon that the study protocol required blood samples be stored at 0°C immediately after sample collection and that the submitted stability data cover and support the blood/plasma sample processing and storage.

REVIEWER'S COMMENT (#1):

The stability issue was raised because of the following reasons:

1. Stability data are required to support the sample storage/processing conditions.
2. There are esterases present in the blood/plasma which can hydrolyze tazarotene.
3. The Japanese PK studies indicated higher tazarotene concentrations in the blood than the U.S. PK studies. Can sample storage/processing conditions result in this disparity?
4. The stability data provided in the original submission (Vol. 72, p. 57) were of

much higher tazarotene concentrations.

In the 6/27/96 amendment, the sponsor provided stability data for samples stored at -80°C and -20°C and, in the 10/9/96 fax (officially submitted on 10/29/96), the room temperature stability data were provided to support the blood/plasma processing and storage. The stability data is now adequate.

The following are the sponsor's responses to the comments listed in the fax dated 6/6/96:

PREVIOUS COMMENT #1-A.
For the removal of the applied dose at 10 hours after application in Study R168-154-8606, the skin wash was monitored using a Geiger Counter. Any area demonstrating high levels of radioactivity was rewiped with gauze pads until the level of radioactivity was deemed acceptable. The sponsor did not indicate what the acceptable level was and how it was determined.

SPONSOR'S RESPONSE:
Initially, the Geiger counter was set at the x10 setting and the washing procedure was performed. Then the sensitivity setting was changed to x1 (10-fold increased sensitivity). Any location passing this higher sensitivity check was considered acceptable and no additional wiping was required.

PREVIOUS COMMENT #1-B:
It is noted that gauze pads wetted with isopropanol were used for skin wash in Study R168-154-8606. Does the use of isopropanol change the drug distribution in skin?

SPONSOR'S RESPONSE:
The skin wash method effectively removed the drug remaining on the skin surface. It is not known conclusively if isopropanol used in skin wash affects the drug distribution in skin. If the isopropanol-wetted gauzes allowed more drug to be absorbed, then one would have seen a secondary absorption hump in the plasma concentration or urinary excretion rate-time profiles. The data show no such kinetics for the plasma concentration or urinary excretion rate-time profiles.

REVIEWER'S COMMENT (#2): The skin wash method seems to focus on effective removal of drug from the skin surface. It is not clear if isopropanol used in skin wash affects the drug distribution in skin. However, the systemic exposure in healthy subjects as determined from this radiolabeled study was in good agreement with another study in which systemic bioavailability of a topical dose was calculated by comparing to the IV dose. (In the latter study, the topical dose was removed by soap and water.)

PREVIOUS COMMENT #1-C:
In Study R168-154-8606, the drug recovered from the first five skin strippings after skin wash was considered drug remained on the skin surface, but the supporting evidence was not

provided.

SPONSOR'S RESPONSE:
The roughness of psoriatic skin requires additional strippings to remove residual gel from the surface. (Reviewer's note: In healthy subjects, the usual practice considers the first two skin stirppings adequate for removing the drug remaining on the skin surface.)

PREVIOUS COMMENT #2:
In the long term psoriasis study (R168-128-8606) a smaller percentage of patients had detectable plasma active metabolite when compared to the short term U.S. or European studies. Please explain this disparity in the plasma concentration between the short term and long term studies. Since instrumental problems were encountered during the plasma sample analysis, this factor should be examined.

SPONSOR'S RESPONSE:
In the short term clinical study, a method with a ng/mL was used for analyzing plasma samples. Later, a method with a ng/mL was developed (for quick throughput) which was used in the long term clinical trials. Because of the lower in the short term studies, there were more quantifiable samples that were detected than in the long term study.

In Study R168-128-8606, instrumental problems were encountered in 3 of the 6 analytical runs. For these three runs, quantitation at ng/mL was not achieved and the was set at ng/mL. Detectable but not quantifiable concentrations between ng/mL were estimated and listed in the report as estimate.

REVIEWER'S COMMENT (#3): In the short term study conducted in the U.S., a method with a ng/mL was used, while a method with a ng/mL was used in the short term study conducted in Europe. The same method was used in the U.S. long term clinical study, but instrumental problems were encountered during the plasma sample analysis and 3 of the 6 analytical runs had a ng/mL. Therefore, the sponsor's explanation to our question is reasonable.

PREVIOUS COMMENT #3:
In future submissions, detailed reports of the in vitro studies should be provided.

SPONSOR'S RESPONSE: The sponsor will make efforts to do this in future submission.

PREVIOUS COMMENT #4:
Based on nonclinical findings, you indicated that the drug, as used clinically, was not teratogenic. However, only one women was included in one out of the eight PK studies even though the sponsor indicated the drug as used topically was not teratogenic based on nonclinical findings.

SPONSOR'S RESPONSE:
Earlier clinical pharmacokinetic studies (R168-150-7997, R168-151-7997 and R168-152-8606) were conducted before all the animal reproductive toxicological studies were concluded. Another two studies involved radiolabeled dose or systemic exposure. Therefore, enrollment in these studies was restricted for precautionary safety reasons.

A pharmacokinetic study in psoriatics is currently ongoing (Study 190168-004). Of the 24 patients enrolled, 13 are female.

In all of the pivotol clinical efficacy trials, women of child bearing potential were allowed to enroll. Of the 1,137 patients enrolled in the phase 3 psoriasis trials and who received drug treatment, 714 were male and 423 were female. Of these female patients, two patients became pregnant while participating in the studies and reported the birth of healthy newborns.

Of 395 patients who were treated with tazarotene gel in the clinical efficacy trials and had their blood monitored for drug levels, 38% were women and stepwise regression analysis showed no effect on the plasma concentration due to gender. The sponsor concluded that the pharmacokinetics after treatment with topical tazarotene in male and female patients are the same.

> *REVIEWER'S COMMENT (#4):* When PK Study 190168-004 is completed, a gender analysis should be performed and the results should be submitted.

PREVIOUS COMMENT #5:
The sponsor is encouraged to develop an in vitro drug release test method and test specifications for the gel formulations.

SPONSOR'S RESPONSE:
The sponsor considers developing such a test would not provide any improvement in the assessment of the product quality beyond those derived from current final product testing methods and specifications.

III. RECOMMENDATION:
From the biopharmaceutics standpoint, the application is approvable. Please communicate Reviewer's Comment #4 to the sponsor.

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD Initialed by Dennis Bashaw, Pharm.D. 10/22/96
FT Initialed by Dennis Bashaw, Pharm.D. 10/31/96

CC:
NDA 20,600
HFD-540 (2 copies)
✓HFD-880 (Division File)
HFD-880 (TL - Bashaw)
✓HFD-880 (Reviewer - Lee)
HFD-340 (Viswanathan)
✓Drug File (Clarence Bott, HFD-870, Pkln 13B31)

MAR 1 4 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-600
PRODUCT: Tazarotene Gel, 0.05%, 0.1%
SPONSOR: Allergan
2525 Dupont Drive, P.O. Box 19534
Irvine, CA 92713-9534

SUBMISSION DATES: 1/17/97

TYPE OF SUBMISSION:
NDA Amendment

REVIEWER: Sue-Chih Lee, Ph.D.

I. BACKGROUND:

Tazarotene is intended for topical treatment of plaque psoriasis and acne vulgaris. It is an acetylenic retinoid and is converted to its active form, tazarotenic acid, in biological systems by de-esterification. The sponsor was issued an approvable letter on December 30, 1996 in which we requested Phase IV commitments to conduct a long term PK study and to provide a gender analysis. In this submission, the sponsor submitted a new study (R190168-004) to address these issues and to revise the labeling.

II. STUDY R190168-004:

An Open-Label Safety, Pharmacokinetics and Efficacy Study of Tazarotene (AGN190168) 0.1% or 0.05% Gel Applied Once Daily For Twelve Weeks in the Treatment of Plaque Psoriasis

INVESTIGATOR AND LOCATION:

OBJECTIVES: To determine the pharmacokinetic profile of the active metabolite (AGN190299) after single and multiple topical applications to psoriatic patients for three months as part of the study objectives.

FORMULATION: To-be-marketed formulations were used.
0.1% gel (Formulation #8606X)
0.05% gel (Formulation #8607X-A)

STUDY DESIGN:

This is a single-center, open-label, parallel-group study. Twenty-four patients (11 M&13 F; mean age: 43±8 yrs; mean wt.: 184±52 lb; mean ht: 66.5±3.7 in; Table 1) with psoriatic involvement between 5% and 15% of the total body surface area participated in the study and 22 completed the study. The involved skin surface area for each individual patient changed with time during treatment. (See Tables II-a, II-b and III-a for body surface area involvement.)

Patients applied tazarotene gel (0.1% or 0.05%) themselves and were instructed to rub a thin layer gently into their skin. Gel was applied to the psoriatic skin once daily for 12 weeks and each dose was removed by showering approximately 12 hours after application. The mean weight of gel applied on the blood sampling days were 2.25 ($\pm$1.31) mg/cm^2 for the 0.1% gel group and 2.18 ($\pm$1.04) mg/cm^2 for the 0.05% gel group. (See Tables III-a and III-b for the doses applied.)

Blood sample collection:

Days 0, 14, 28, and 56: 0 (pre-dose), 3, 6, 9, 12, 16, 20 and 24 hours
Day 84: 0 (pre-dose), 3, 6, 9, 12, 16, 20, 24, 36, 48, 60 and 72 hours
2 weeks after the last dose: one blood sample was collected.

Comment: The dose (in terms of amount of gel per cm^2) and involved skin surface area varied from patient to patient and from day to day within a patient.

ASSAY:

DATA ANALYSIS:

The distribution half-life was calculated from the data between 16 and 24 hours following the preceding dose. The terminal half-life was calculated from the plasma concentration time profile between 36 and 72 hours following the last dose.

Due to sampling difficulties, one blood sample could not be collected (Patient Day 28, 3 hr); therefore, the average of the plasma concentrations at the time point before and the time point after was used.

The bioavailability was estimated from dose and AUC values for this study and a previous IV infusion study, assuming the dose was quantitatively metabolized from tazarotene to the active metabolite and that clearance was constant in both studies.

The data were also analyzed by gender.

RESULTS:

Out of the 22 patients who completed the study, 12 (4 M & 8 F) received the 0.1% gel and 10 (7M & 3F) received the 0.05% gel.

0.1% gel: (Tables IV, VIII and X)

After the first dose, the mean peak plasma concentration (Cmax) of the active metabolite was 0.103$\pm$0.071 ng/mL occurring at 13.9$\pm$4.2 hours postdose. The mean plasma concentration decreased to 0.069$\pm$0.047 ng/mL by 24 hours after the first dose with a distribution half-life of 12.5$\pm$16.6 hours. The mean $AUC_{0\text{-}24\ hr}$ was 1.68$\pm$1.18 ng.hr/mL.

After the Day 14 dose, the mean Cmax reached 1.20±1.14 ng/mL (~12-fold of first dose) occurring at 6.00±1.81 hours postdose. The mean plasma concentration was 0.273±0.238 ng/mL by 24 hours after the first dose with a distribution half-life of 9.22±2.44 hours. The mean $AUC_{0\text{-}24\ hr}$ was 16.5±15.6 ng.hr/mL (~10-fold of first dose) which was equivalent to about 5.33±3.11% of the applied dose.

By Day 84, the mean Cmax was 0.83±1.22 ng/mL and the mean $AUC_{0\text{-}24}$ was 11.8±16.0 ng.hr/mL (equivalent to about 3.87±3.13% of the applied dose). The distribution half-life was similar from Day 14 to Day 84 ranging from hours, and the terminal half-life after the last dose was 16.7±6.0 hours.

The highest plasma concentration observed in an individual patient during the study was ng/mL (Patient on Day 84 at 6 hours postdose). Two weeks after the last dose, plasma concentrations ranged from BLQ (n=5) to 0.032 ng/mL.

0.05% gel: (Table IV, VII and IX)
After the first dose, the mean Cmax of the active metabolite was 0.091±0.106 ng/mL occurring at 11.3±4.9 hours postdose. The plasma concentration decreased to 0.037±0.033 ng/mL by 24 hours after the first dose with a distribution half-life of 12.8±7.8 hours. The mean $AUC_{0\text{-}24\ hr}$ was 1.39±1.63 ng.hr/mL.

After the Day 14 dose, the mean Cmax reached 0.348±0.219 ng/mL (~4-fold) occurring at 7.91±2.02 hours postdose. The plasma concentration decreased to ng/mL by hours after the dose with a distribution half-life of hours. The mean $AUC_{0\text{-}24\ hr}$ was 4.96±3.12 ng.hr/mL (~3.5-fold of first dose) which was equivalent to about 2.60±1.69% of the applied dose.

By Day 84, the mean Cmax was 0.454±0.775 ng/mL and the mean $AUC_{0\text{-}24\ hr}$ was 5.74±8.45 ng.hr/mL (equivalent to about 1.80±0.81% of the applied dose). The distribution half-life was similar from Day 14 to Day 84 ranging from hours, and the terminal half-life after the last dose was hours.

The highest plasma concentration observed in an individual patient during the study was 2.58 ng/mL (Patient on Day 84 at 9 hours postdose). Two weeks after the last dose, plasma concentrations ranged from BLQ (n=5) to 0.012 ng/mL.

Both 0.1% and 0.05% gels:
The elimination half-life remained unchanged throughout the 3-month treatment. Up to Day 14, increase in systemic absorption was observed. No further accumulation was observed after Day 14 (Figures 1 & 2).

Comparison by gender:
Tables V & VI were provided to compare the PK parameters between male and female patients. The sponsor made no discussion of the results stating that definitive results could not be derived from the study because of the small number of patients in the subgroups.

III. COMMENTS:

A. GENERAL COMMENTS:

1. In this study, the gel was applied by patients themselves without controlling the doses which actually varied from patient to patient and from day to day within a patient. (The involved skin surface area also varied from day to day within a patient.) This is not considered a rigorous PK study.

2. The elimination half-life after 3-month treatment as observed in this study was similar to that found in the previous studies. Elimination rate of the active metabolite did not change after prolonged treatment.

3. To assess the changes in systemic absorption of tazarotene as the treatment went on, the Cmax and AUC values within individual patients (rather than the mean values) on various dosing days were compared, taking into account the changes in doses. By inspecting the data this way, it was found that the results from this study was consistent with the previous findings (Study R168-153-8606) that systemic absorption increased significantly from Day 1 to Day 14 and more or less stabilized from then on. The absorption (after dose adjustment) increased at a later time in some patients to 2-fold of Day 14 values, while it decreased in some others possibly due to changes in skin conditions. The fact that dose varied from day to day and was only determined on the blood sample collection days confounded this analysis, so did the variation in the involved skin surface area within each individual patient. However, the analysis did provide a qualitative measure of changes in systemic absorption after long term use. Therefore, this study is considered acceptable and no new long term study will be requested.

4. The general PK characteristics of the product as observed from this study were similar to the findings of a previous study. The extent of systemic absorption was lower in this study mostly likely to be due to differences in the study design. In the previous 14-day study (R168-153-8606), fixed doses (approximately 2 mg/cm^2) were applied daily by nursing staff to the same lesions and were left uncovered by clothing for 2 hours after dosing, while the current study had uncontrolled dosing.

5. No definitive comparison between genders could be made. This is because of the small number of patients in each subgroup. Another factor was the uncontrolled doses which resulted in greater variations. The sponsor should submit new information on gender analysis when such data becomes available.

6. There have been no PK studies in acne patients. (The percutaneous absorption through acne lesions as compared to psoriatic lesions is not known.) This fact should be considered if the pregnancy category will be determined separately for each use.

B. LABELING COMMENTS:

1. The labeling under Pharmacokinetics should be revised as follows:

1 Page (5)
Deleted

IV. RECOMMENDATION:

From the biopharmaceutics standpoint, the application is approvable provided that the PK section of the labeling is revised accordingly. Labeling comment #1 and general comment #5 should be communicated to the sponsor. Please convey general comment #6 and labeling comments #2 and 3 to the Division of Dermatological and Dental Drug Products.

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD Initialed by Dennis Bashaw, Pharm.D. _____
FT Initialed by Dennis Bashaw, Pharm.D. Edb 5/14/97

CC:
NDA 20,600
HFD-540 (2 copies)
HFD-880 (Division File)
HFD-880 (TL - Bashaw)
HFD-880 (Reviewer - Lee)
HFD-340 (Viswanathan)
Drug File (Barbara Murphy, CDR)

Table I. Summary of Patient Demographics and Characteristics: Sex, Date of Birth, Weight, Height and Frame Size.

Patient	Dose Group (% Gel)	Sex	Age (years)	Weight (lb)	Height (in.)	Frame Size
	0.1	Male				Medium
	0.1	Male				Medium
	0.1	Female				Large
	0.1	Female				Small
	0.1	Female				Small
	0.05	Male				Large
	0.05	Male				Medium
	0.05	Male				Large
	0.05	Male				Medium
	0.05	Male				Medium
	0.1	Male				Medium
	0.1	Female				Medium
	0.1	Female				Medium
	0.1	Female				Medium
	0.1	Female				Medium
	0.05	Female				Small
	0.05	Female				Medium
	0.05	Female				Small
	0.05	Female				Large
	0.05	Female				Large
	0.1	Female				Small
	0.05	Male				Medium
	0.05	Male				Small
	0.1	Male				Medium
		Mean:	43	184	66.5	
		S.D.	8	52	3.7	
		n:	24	24	24	

0.1% : 4M + 8F

0.05% : 4M + 5F → 7M + 3F

Table II-a. Summary of Body Surface Area of Psoriatic Involvement[a]

	0.05% Gel			0.1% Gel			Combined 0.05% and 0.1% Gel		
	Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n
Day 0	7.50	3.63	12	6.92	2.94	12	7.21	3.24	24
Day 14	6.73	4.27	11	6.25	3.55	12	6.48	3.82	23
Day 28	6.90	4.43	10	5.42	3.70	12	6.09	4.02	22
Day 56	6.40	4.01	10	4.17	2.66	12	5.18	3.45	22
Day 84	6.40	4.14	10	4.67	5.18	12	5.45	4.71	22

[a] Expressed as percentage of total body surface area

Table II-b

~~Appendix I.~~ Individual Body Surface Area Involvement by Patient [a]

0.05% Gel

Patient # / Day	
Day 0	
Day 14	
Day 28	
Day 56	
Day 84	

0.1% Gel

Patient # / Day	mean ± SD
Day 0	6.9 ± 2.9
Day 14	6.3 ± 3.5
Day 28	5.4 ± 3.7
Day 56	4.2 ± 2.7
Day 84	4.7 ± 5.2

[a] Expressed as percentage of total body surface area
ND = No data

Table III-a Summary of Dose Applied and Dosing Rate.

Patient	Gel Conc. (%)	Weight (kg)	Height (in.)	Total Body Surface Area (m^2)	Mean Dosed Area (cm^2)	Mean Weight of Gel Applied[a] (g)	Mean Tazarotene Dosage (µg/kg)	Mean Tazarotene Dosage (µg/cm^2)	Day 84 Dosed Area (cm^2)
					685	3.56	33.2	5.20	
					1069	3.30	41.0	3.09	
					677	1.92	22.5	2.84	
					1248	1.82	35.1	1.46	
					935	0.980	16.3	1.05	
					935	1.30	17.2	1.39	
					893	0.860	10.3	0.963	
					670	1.78	19.1	2.66	
					1112	3.02	28.6	2.71	
					344	0.640	8.80	1.86	
					2161	1.12	23.7	0.518	
					912	3.03	37.5	3.32	
					3660	11.3	40.5	1.54	
					1172	5.40	31.1	2.30	
					1484	4.22	23.2	1.42	
					907	1.82	11.9	1.00	
					929	1.56	9.64	0.839	
					411	0.500	4.78	0.609	
					984	1.60	11.9	0.813	
					1120	3.40	26.9	1.52	
					1040	1.08	4.75	0.519	
					1361	2.00	7.43	0.735	
					1100	1.66	8.61	0.755	
					2385	4.74	36.5	0.994	
0.1% Gel									
	Mean	78.6	65.2	1.85	970	1.94	24.4	2.25	872
	S.D.	18.9	2.5	0.21	446	1.03	10.6	1.31	740
	n	12	12	12	12	12	12	12	11
0.05% Gel									
	Mean	88.9	67.9	2.00	1379	3.27	18.1	1.09	1381
	S.D.	27.9	4.2	0.31	855	2.96	12.9	0.52	994
	n	12	12	12	12	12	12	12	10
Combined 0.1% & 0.05% Gels									
	Mean	83.8	66.5	1.92	1175	2.61	21.3	1.67	
	S.D.	23.9	3.7	0.27	699	2.27	12.0	1.14	
	n	24	24	24	24	24	24	24	

[a] Mean weight of gel applied on the blood sampling days

Table III-b.

~~Appendix 2.~~ Listing of Dose Applied by Patient [a]

0.05% Gel

Patient #	Mean ± SD
Day	
Day 0	2.8 ± 3.1 (n=12)
Day 14	3.4 ± 2.6 (n=11)
Day 28	3.6 ± 3.5 (n=10)
Day 56	2.8 ± 3.0 (n=10)
Day 84	4.26 ± 5.13 (n=10)

0.1% Gel

Patient #	Mean ± SD
Day	
Day 0	1.4 ± 1.1
Day 14	1.7 ± 1.2
Day 28	2.2 ± 1.7
Day 56	1.7 ± 0.9 (n=11)
Day 84	1.9 ± 1.2 (n=11)

[a] Weight of gel applied (g)
ND = No data

Table IV. Summary of the pharmacokinetic parameters of AGN 190299 following topical administration of tazarotene 0.05% or 0.1% gel daily to psoriatic patients for twelve weeks.[a]

Parameter (Units)	0.05% Gel					0.1% Gel				
	Day 0	Day 14	Day 28	Day 56	Day 84	Day 0	Day 14	Day 28	Day 56	Day 84
Dose applied[b]	1.42	1.72	1.80	1.39	2.13 1.69±0.30	1.90	1.82	2.23	1.69	1.88 1.90 ± 0.20
C_{max} (ng/mL)	0.0910 (0.1060)	0.348 (0.219)	0.490 (0.535)	0.295 (0.360)	0.454 (0.775)	0.103 (0.071)	1.20 (1.14)	1.07 (1.05)	0.588 (0.546)	0.830 (1.220)
t_{max} (hr)	11.3 (4.9)	7.91 (2.02)	7.50 (2.55)	11.2 (5.4)	8.70 (2.63)	13.9 (4.2)	6.00 (1.81)	6.75 (3.41)	7.64 (2.80)	6.82 (2.36)
AUC_{0-24} (ng•hr/mL)	1.39 (1.63)	4.96 (3.12)	6.73 (7.44)	4.93 (5.84)	5.74 (8.45)	1.68 (1.18)	16.5 (15.6)	15.0 (14.6)	8.54 (7.20)	11.8 (16.0)
AUC_{0-INF} (ng•hr/mL)	NA NA	NA NA	NA NA	NA NA	8.90 (11.90)	NA NA	NA NA	NA NA	NA NA	16.0 (20.5)
Terminal k (hr^{-1})	NA NA	NA NA	NA NA	NA NA	0.0450 (0.0110)	NA NA	NA NA	NA NA	NA NA	0.0414 (0.0150)
Terminal $t_{1/2}$ (hr)	NA NA	NA NA	NA NA	NA NA	15.4 (3.8)	NA NA	NA NA	NA NA	NA NA	16.7 (6.0)
Distribution k (hr^{-1})	0.0541 (0.0324)	0.0846 (0.0154)	0.0824 (0.0237)	0.0885 (0.0249)	0.0690 (0.0347)	0.0554 (0.0571)	0.0751 (0.0196)	0.103 (0.042)	0.0816 (0.0171)	0.0755 (0.0308)
Distribution $t_{1/2}$ (hr)	12.8 (7.8)	8.19 (1.49)	8.41 (2.39)	7.83 (2.26)	10.0 (4.9)	12.5 (16.6)	9.22 (2.44)	6.72 (2.94)	8.50 (1.78)	9.18 (3.75)
Bioavailability (%)	0.892 (1.110)	2.60 (1.69)	3.65 (2.73)	2.47 (1.02)	1.80 (0.81)	0.644 (0.320)	5.33 (3.11)	4.57 (3.12)	3.49 (1.94)	3.87 (3.13)

[a] Mean (S.D.), n=12 for each gel strength

[b] mg tazarotene

NA Not applicable

Table V Summary of the Pharmacokinetic Parameters of AGN 190299 Following Topical Administration of tazarotene 0.05% Gel, Separated by Gender

Parameter (Units)	Male [a]					Female [b]				
	Day 0	Day 14	Day 28	Day 56	Day 84	Day 0	Day 14	Day 28	Day 56	Day 84
Dose applied [c]	1.85	2.25	2.48	1.75	2.63	0.800	0.790	0.200	0.535	0.965
C_{max} (ng/mL)	0.0854 (0.0600)	0.459 (0.198)	0.631 (0.586)	0.396 (0.394)	0.612 (0.896)	0.0988 (0.1590)	0.153 (0.054)	0.162 (0.165)	0.0610 (0.0480)	0.0870 (0.0940)
t_{max} (hr)	10.4 (3.2)	7.71 (1.60)	7.29 (1.60)	9.60 (3.51)	8.57 (2.70)	12.6 (6.8)	8.25 (2.87)	8.00 (4.58)	15.0 (7.9)	9.00 (3.00)
AUC_{0-24} (ng•hr/mL)	1.28 (0.92)	6.58 (2.69)	9.10 (7.82)	6.60 (6.33)	7.66 (9.60)	1.54 (2.44)	2.11 (1.02)	1.19 (0.40)	1.04 (0.76)	1.26 (1.40)
AUC_{0-INF} (ng•hr/mL)	NA NA	NA NA	NA NA	NA NA	10.7 (13.1)	NA NA	NA NA	NA NA	NA NA	2.72 (2.25)
Terminal k (hr^{-1})	NA NA	NA NA	NA NA	NA NA	0.05 0.01	NA NA	NA NA	NA NA	NA NA	0.03 0.01
Terminal $t_{1/2}$ (hr)	NA NA	NA NA	NA NA	NA NA	14.3 (2.84)	NA NA	NA NA	NA NA	NA NA	21.1 (3.24)
Distribution k (hr^{-1})	0.0600 (0.0300)	0.0800 (0.0200)	0.0800 (0.0200)	0.0800 (0.0300)	0.0700 (0.0400)	0.0300 (0.0500)	0.0900 (0.0100)	0.0800 (0.0300)	0.100 (0.020)	0.0600 (0.0300)
Distribution $t_{1/2}$ (hr)	11.4 (5.0)	8.27 (1.86)	8.29 (2.25)	8.17 (2.72)	9.63 (4.91)	16.3 (25.1)	8.06 (0.83)	8.70 (1.33)	6.82 (1.16)	11.1 (2.8)
Bioavailability (%)	0.591 (0.154)	2.84 (1.79)	2.88 (1.39)	2.88 (0.80)	2.12 (0.70)	1.31 (1.73)	2.19 (1.66)	5.46 (4.57)	1.51 (0.89)	1.04 (0.48)

[a] n = 7 Male

[b] n = 5 Female (4 on Day 14, 3 after Day 14)

[c] mg tazarotene

Table VI Summary of the Pharmacokinetic Parameters of AGN 190299 Following Topical Administration of tazarotene 0.1% Gel, Separated by Gender

Parameter (Units)	Male [a]					Female [b]				
	Day 0	Day 14	Day 28	Day 56	Day 84	Day 0	Day 14	Day 28	Day 56	Day 84
Dose applied [c]	2.48	2.45	3.58	2.67	2.63	1.61	1.50	1.55	1.33	1.60
C_{max} (ng/mL)	0.115 (0.076)	1.37 (0.77)	1.33 (0.87)	0.952 (0.913)	0.676 (0.490)	0.0970 (0.0727)	1.11 (1.33)	0.940 (1.160)	0.452 (0.330)	0.888 (1.430)
t_{max} (hr)	12.5 (4.7)	5.25 (1.50)	6.00 (0.00)	6.00 (0.00)	6.00 (0.00)	14.6 (4.0)	6.38 (1.92)	7.13 (4.22)	8.25 (3.11)	7.13 (2.75)
AUC_{0-24} (ng•hr/mL)	1.92 (1.25)	16.8 (9.3)	18.1 (11.0)	12.7 (11.5)	9.70 (6.80)	1.56 (1.21)	16.3 (18.5)	13.4 (16.6)	7.00 (5.14)	12.6 (18.8)
AUC_{0-INF} (ng•hr/mL)	NA NA	NA NA	NA NA	NA NA	12.9 (8.3)	NA NA	NA NA	NA NA	NA NA	17.20 (23.90)
Terminal k (hr^{-1})	NA NA	NA NA	NA NA	NA NA	0.0380 0.0082	NA NA	NA NA	NA NA	NA NA	0.0427 0.0171
Terminal $t_{1/2}$ (hr)	NA NA	NA NA	NA NA	NA NA	18.2 (2.8)	NA NA	NA NA	NA NA	NA NA	16.2 (6.4)
Distribution k (hr^{-1})	0.0792 (0.0909)	0.0738 (0.0066)	0.0980 (0.0252)	0.0852 (0.0122)	0.0674 (0.0306)	0.0353 (0.0307)	0.0758 (0.0242)	0.106 (0.050)	0.0802 (0.0191)	0.0785 (0.0324)
Distribution $t_{1/2}$ (hr)	8.80 (18.60)	9.40 (0.84)	7.10 (1.83)	8.10 (0.16)	10.3 (3.1)	16.6 (10.8)	9.10 (2.97)	6.60 (3.46)	8.60 (2.08)	8.80 (5.65)
Bioavailability (%)	0.495 (0.202)	4.84 (2.53)	3.33 (1.05)	2.91 (1.80)	2.46 (1.68)	0.719 (0.353)	5.58 (3.50)	5.20 (3.68)	3.70 (2.07)	4.40 (3.47)

[a] n = 4 Male (n=3 on Days 56 & 84)
[b] n = 8 Female
[c] mg tazarotene

Table VII

~~Appendix 3.~~ Listing of Plasma Concentrations versus Time of AGN 190299 by Patient following Administration of the 0.05% Gel [a]

Day	Time Point	Patient #	Mean	S.D.	n
0			0.0000	NC	12
0			0.0291	0.0322	12
1			0.0733	0.0996	12
1			0.0888	0.1062	12
1			0.0833	0.1066	12
1			0.0670	0.0793	12
1			0.0454	0.0439	12
1			0.0374	0.0332	12
14			0.0903	0.0603	11
14			0.182	0.124	11
15			0.308	0.191	11
15			0.319	0.223	11
15			0.253	0.156	11
15			0.192	0.124	11
15			0.137	0.090	11
15			0.0976	0.0628	11
28			0.133	0.116	10
28			0.290	0.304	10
29			0.440	0.557	10
29			0.415	0.527	10
29			0.336	0.368	10
29			0.251	0.264	10
29			0.167	0.169	10
29			0.123	0.115	10

[a] ng/mL
NC = Not calculable
ND = No data
BLQ = Below the limit of quantitation

Table VII

Appendix 3. Listing of Plasma Concentrations versus Time of AGN 190299 by Patient following Administration of the 0.05% Gel [a]
Cont.

Day	Time Point	Patient #	Mean	S.D.	n
56			0.110	0.118	10
56			0.160	0.161	10
57			0.269	0.341	10
57			0.288	0.362	10
57			0.273	0.359	10
57			0.220	0.269	10
57			0.144	0.149	10
57			0.100	0.090	10
84			0.0436	0.0299	10
84			0.166	0.231	10
85			0.378	0.597	10
85			0.433	0.774	10
85			0.283	0.366	10
85			0.220	0.310	10
85			0.161	0.219	10
85			0.112	0.146	10
85			0.0595	0.0710	9
85			0.0341	0.0386	9
85			0.0252	0.0307	7
85			0.0168	0.0217	7
98			0.00868	0.00290	5

[a] ng/mL,
ND = No data
BLQ = Below the limit of quantitation

Table VIII

Appendix 4. Listing of Plasma Concentrations versus Time of AGN 190299 by Patient following Administration of the 0.1% Gel [a]

Day	Time Point	Patient #	Mean	S.D.	n
0			0.0000	NC	12
0			0.0259	0.0305	12
1			0.0625	0.0570	12
1			0.0856	0.0704	12
1			0.0986	0.0707	12
1			0.0925	0.0591	12
1			0.0755	0.0474	12
1			0.0689	0.0470	12
14			0.401	0.468	12
14			0.925	0.815	12
15			1.17	1.13	12
15			0.866	0.808	12
15			0.736	0.771	12
15			0.538	0.534	12
15			0.423	0.461	12
15			0.273	0.238	12
28			0.318	0.424	12
28			0.732	0.816	12
29			1.04	1.06	12
29			0.871	0.880	12
29			0.730	0.721	12
29			0.549	0.464	12
29			0.333	0.305	12
29			0.252	0.221	12

[a] ng/mL
ND = No data
BLQ = Below the limit of quantitation

Table VIII

Appendix 4. Listing of Plasma Concentrations versus Time of AGN 190299 by Patient following Administration of the 0.1% Gel [a]
Cont.

Day	Time Point	Patient #	Mean	S.D.	n
56			0.146	0.167	11
56			0.386	0.387	11
57			0.539	0.537	11
57			0.515	0.470	11
57			0.447	0.394	11
57			0.319	0.238	11
57			0.209	0.148	11
57			0.163	0.117	11
84			0.231	0.283	11
84			0.447	0.572	11
85			0.815	1.229	11
85			0.707	1.006	11
85			0.602	0.818	11
85			0.436	0.573	11
85			0.316	0.407	11
85			0.216	0.264	11
85			0.0969	0.1167	11
85			0.0611	0.0623	11
85			0.0335	0.0308	10
85			0.0228	0.0204	10
98			0.0127	0.0099	7

[a] ng/mL
ND = No data
BLQ = Below the limit of quantitation

Table IX

Appendix 7. Listing of Pharmacokinetic Parameters of AGN 190299 by Patient for the 0.05% Gel

	Patient #
C_{max} (ng/mL)	Day 0 Day 14 Day 28 Day 56 Day 84
t_{max} (hr)	Day 0 Day 14 Day 28 Day 56 Day 84
AUC_{0-24} (ng•hr/mL)	Day 0 Day 14 Day 28 Day 56 Day 84
AUC_{0-INF} (ng•hr/mL)	Day 84
Terminal k (hr^{-1})	Day 84
Terminal $t_{1/2}$ (hr)	Day 84

NC = Not Calculable
ND = No Data

Table IX

Appendix 7 (cont'd). **Listing of Pharmacokinetic Parameters of AGN 190299 by Patient for the 0.05% Gel**

	Patient #
Distribution k (hr^{-1})	Day 0 Day 14 Day 28 Day 56 Day 84
Distribution $t_{1/2}$ (hr)	Day 0 Day 14 Day 28 Day 56 Day 84
Bioavailability (%)	Day 0 Day 14 Day 28 Day 56 Day 84

NC = Not Calculable
ND = No Data

Table X.

Appendix 8. Listing of Pharmacokinetic Parameters of AGN 190299 by Patient for the 0.1% Gel

	Patient #
C_{max} (ng/mL)	Day 0 Day 14 Day 28 Day 56 Day 84
t_{max} (hr)	Day 0 Day 14 Day 28 Day 56 Day 84
AUC_{0-24} (ng•hr/mL)	Day 0 Day 14 Day 28 Day 56 Day 84
AUC_{0-INF} (ng•hr/mL)	Day 84
Terminal k (hr^{-1})	Day 84
Terminal $t_{1/2}$ (hr)	Day 84

ND = No Data

Table X

Appendix 8 (cont'd). Listing of Pharmacokinetic Parameters of AGN 190299 by Patient for the 0.1% Gel

	Patient #
Distribution k (hr^{-1})	Day 0 Day 14 Day 28 Day 56 Day 84
Distribution $t_{1/2}$ (hr)	Day 0 Day 14 Day 28 Day 56 Day 84
Bioavailability (%)	Day 0 Day 14 Day 28 Day 56 Day 84

NC = Not Calculable
ND = No Data

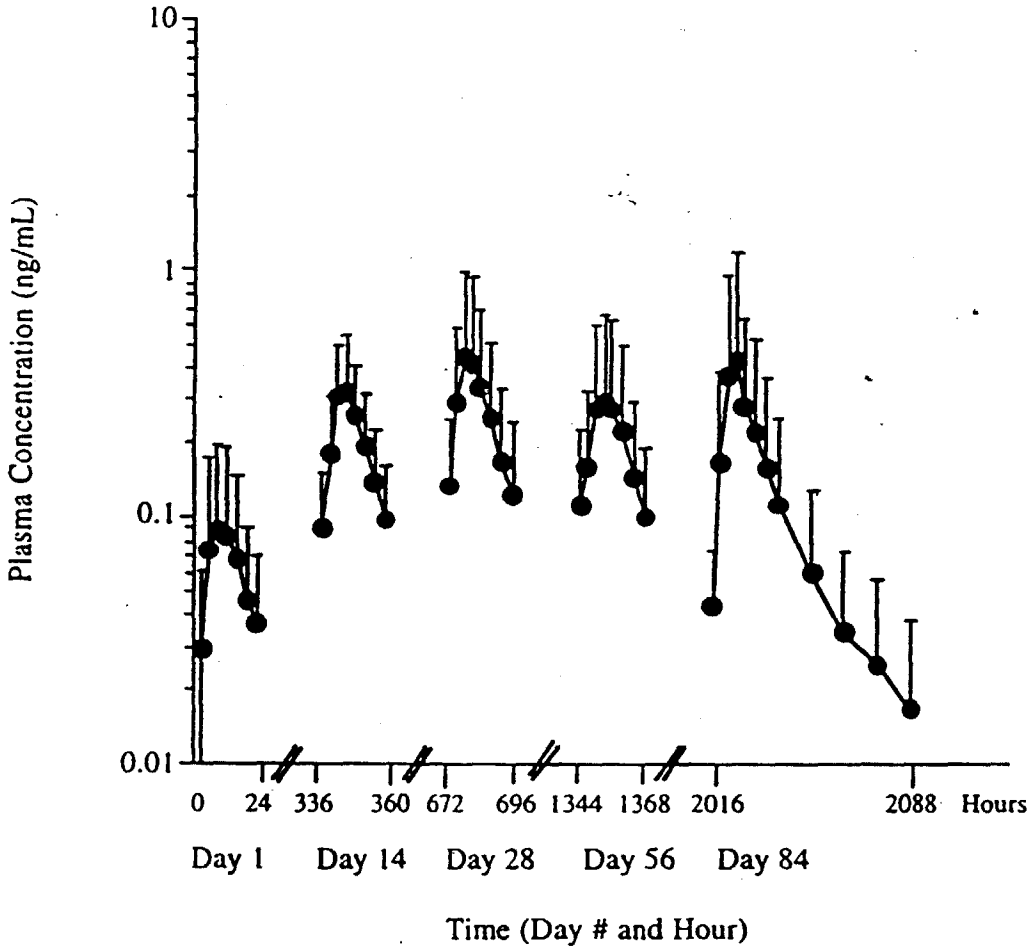


Figure 1 Plasma AGN 190299 concentration versus time profile following once-daily administration of tazarotene (AGN 190168) 0.05 % gel for twelve weeks. Cumulative time in hours after first dose. Mean ± S.D.: Logarithmic Plot.

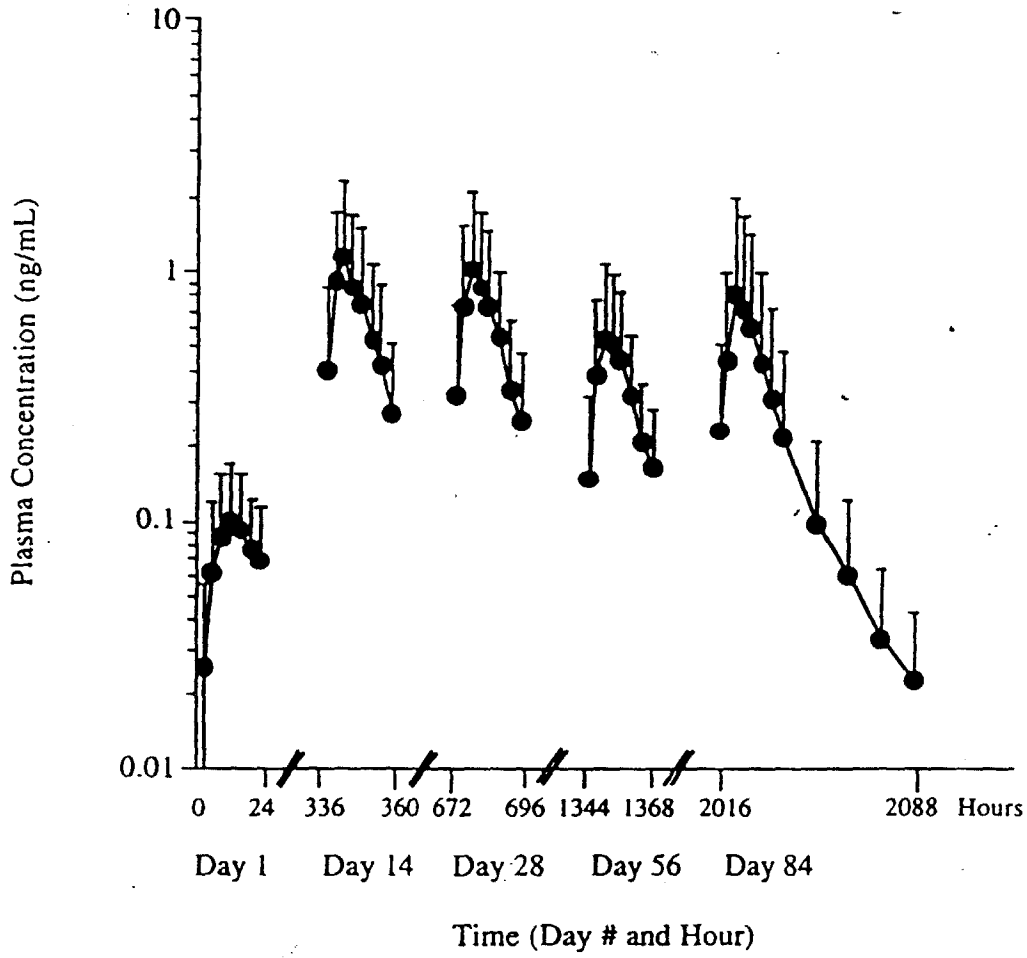


Figure 2 Plasma AGN 190299 concentration versus time profile following once-daily administration of tazarotene (AGN 190168) 0.1 % gel for twelve weeks. Cumulative time in hours after first dose. Mean ± S.D.: Logarithmic Plot.