

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-600

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

APR 26 1996

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS 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:

NME, Original NDA, 1S

SUBMISSION DATES:

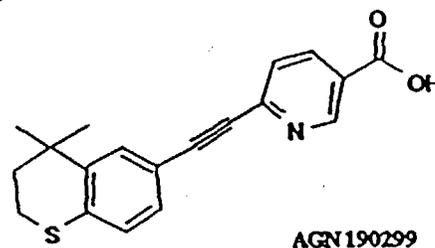
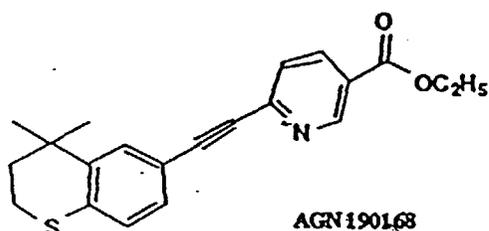
06/16/95, 06/22/95, 10/30/95

03/11/96, 03/15/96, 04/05/96

REVIEWER: Sue-Chih Lee, Ph.D.

I. BACKGROUND:

Tazarotene (AGN 190168) is intended for topical treatment of plaque psoriasis and acne vulgaris. It is a member of the acetylenic retinoids and is converted to its active form, tazarotenic acid (AGN 190299), in biological systems by deesterification.



The exact mechanism of action of this compound is unknown. However, retinoids are fundamental mediators of cell proliferation and differentiation, and some are currently used for a number of indications characterized by abnormal cellular growth. The sponsor states that tazarotene represents the first topical retinoid useful for the treatment of psoriasis. The fact that it will be used topically may provide an advantage by avoiding the most concerning adverse events associated with systemic retinoids such as mucocutaneous reactions, serum lipid elevation and teratogenicity. The drug product has not been approved in any country.

Included in the Human Pharmacokinetics section are:

- i) in vivo percutaneous absorption/PK studies in healthy subjects and psoriatic patients,
- ii) therapeutic drug level monitoring in both psoriatic and acne patients, and
- iii) in vitro studies related to percutaneous absorption and metabolism of tazarotene.

II. FORMULATION and DOSAGE REGIMEN:

The formulations of the gels intended for marketing (Formulation #8606X for 0.1% gel and #8607X-A for 0.05% gel) are given in the table below. Initially, the manufacture involved the nonaqueous to aqueous phase addition. The new process has the aqueous phase added to the organic phase instead. In early development stage, Formulations #7997X (0.1% gel) and #8225X (0.05% gel) were used, which differed in that _____ was used as the

The gel product is intended for once daily application. The clinical dose for the treatment of psoriasis to 20% of the body surface area of a 70 Kg person is approximately 0.1 mg tazarotene/kg/day (or 0.1 g gel/kg/day) based on a dosing density of 2 mg/cm² and a body surface area of 1.75 m².

Components and composition:

Ingredient	% w/w	
	0.1 % Gel (#8606X)	0.05% Gel (#8607X-A)
√Tazarotene		
• Benzyl Alcohol		
• Ascorbic Acid		
• BHA		
• BHT		
Disodium EDTA		
• PEG 400		
• Hexylene Glycol		
• Carbomer 934P		
√Tromethamine		
• Poloxamer 407		
• Polysorbate 40		
√Purified Water		

III. SUMMARY OF IN VIVO STUDIES:

A. PERCUTANEOUS ABSORPTION:

The following results were obtained from studies with a dose of approximately 2 mg/cm² and a dose exposure time of 10 to 12 hours.

In healthy subjects, the systemic absorption after a single topical application was less than 1% ($0.55 \pm 0.22\%$) of the applied dose without occlusion (n=6), and approximately 5% ($5.30 \pm 1.99\%$) under occlusion (n=6).

In psoriatic patients, the systemic absorption appears greater and increases more substantially upon multiple topical dosing when compared to the healthy subjects. Large intersubject variation was observed and the skin condition appeared to greatly affect the extent of percutaneous absorption.

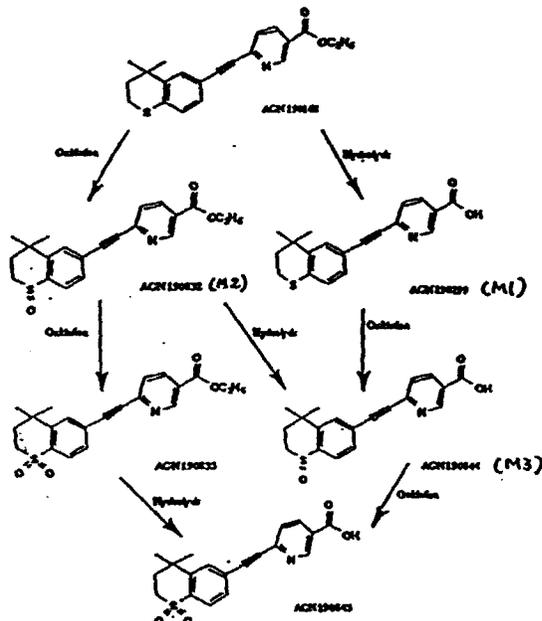
After a single topical dose in psoriatic patients without occlusion, the systemic absorption was found to be $0.76 \pm 0.67\%$ in one study (n=6) but it could be higher (3%) as indicated by

another study (n=5). As much as 15% of the applied dose may be absorbed after repeated dosing in the patients without occlusion (n=5).

Whether with or without occlusion, about 5 to 6% of the applied dose was found in the stratum corneum and about 2% in the viable epidermis-dermis layer.

B. METABOLISM:

Tazarotene is rapidly metabolized upon reaching the systemic circulation. The metabolic pathways of tazarotene include ester hydrolysis to form the free acid and oxidation to form sulfoxide and sulfone metabolites. The primary metabolites of tazarotene consist of the free acid (AGN 190299, the active metabolite) in plasma, and the sulfoxide of the free acid (AGN 190844, 94±8%) in urine. In fecal excretion, polar metabolites (59%) (one of which was identified as an oxygenated derivative of AGN190299) were found in addition to the above 2 metabolites.



C. EXCRETION:

In studies using radiolabeled drug, both urinary and fecal excretion pathways were found to be equally important. In one study following a single topical administration (Formulation #7997X-C14) for 10 hours under occlusion to 6 healthy subjects, 2.61±0.81% of the dose was excreted in the urine and 2.69±1.23% excreted in the stool. In another study, following a single topical administration (Formulation #8606X-C14) for 10 hours without occlusion to 6 psoriatic patients, 0.329±0.228% of the dose was recovered from urine and 0.426±0.472% recovered from stool.

D. PLASMA CONCENTRATIONS:

i) PK studies:

The results of eight PK studies are presented in the following table. In a study (R168-153-8606) conducted in 5 psoriatic patients with 8-18% involved skin surface area, the mean C_{max} and AUC of both tazarotene and the active metabolite were found to increase along with a decrease in T_{max} upon repeated dosing and approached a plateau by Dose 8. The C_{max} and AUC_{0-inf} values for Dose 14 were 0.185±0.084 ng/mL and 1.14±0.44 ng.hr/mL,

respectively, for tazarotene and 12.0 ± 7.6 ng/mL and 105 ± 55 ng.hr/mL, respectively, for the active metabolite. The highest individual plasma concentration of the active metabolite found in this study was ng/mL. These C_{max} and AUC values were much higher than those observed in a multiple-dose study in healthy subjects (Study R168-152-8606).

ii) Therapeutic drug monitoring in Phase III clinical trials using formulation 7997X or 8606X yielded the following results:

1) U.S. Studies for psoriasis - 4 trials, total of 283 drug-treated patients

Psoriatic skin: 1-20% BSA

Dose: 0.1% or 0.05% gel, once daily for up to 12 weeks

Assay

Results:

2) European studies for psoriasis - total of 191 drug-treated patients

Psoriatic skin: 1-20% BSA

Dose: 0.1% or 0.05% gel, once daily for up to 12 weeks

Assay

C_p:

3) U.S. one-year study in psoriatic patients -

Psoriatic skin: 1-20% BSA

Dose: 0.1% or 0.05% gel, once daily for up to one year

A total of 101 patients completed the study.

Plasma tazarotene concentration:

Three patients had detectable concentrations; All were below 1 ng/mL.

Plasma concentration of the active metabolite:

Detected in 31 patients (18 patients on 0.1% gel and 13 on 0.05% gel).

Four patients had concentrations greater than 1 ng/mL.

Highest concentration: ng/mL.

4) U.S. studies for acne - total of 92 drug treated patients

Dose: 0.1% or 0.05% gel, once daily for up to 12 weeks

Results: 4% (4/92) had measurable tazarotene

14% (13/92) had measurable active metabolite concentrations

Highest concentration: ng/mL

Some of the above studies were analyzed to show that the median concentrations of the active metabolite rose at Week 4 to 0.128 ng/mL for 0.1% gel and then fell to approximately one half on weeks 8 and 12. (The median sampling time was 15 to 16 hours post-dose.)

Summary of Phase I PK Results:

Study#*	Study Design	Tazarotene Cmax, ng/mL	Active Metabolite (M1)			
			Cmax ng/mL	AUC ng.h/mL	Tmax hr	T _{1/2} hr
PERCUTANEOUS ABSORPTION STUDIES USING ¹⁴C-TAZAROTENE:						
R168-150-7997	Healthy, n=6 0.1% gel, single dose, 2 g/800 cm ² 10 hr exposure, occluded	total radioactivity equiv. to				
R168-154-8606	Psoriatic patients, n=6 0.1% gel, single dose, 2.28±0.19g over 5% BSA, 10 hr exposure, unoccluded	total radioactivity equiv. to:				
SINGLE DOSE STUDIES						
R168-712-7997	Healthy, n=6 (Japanese) 0.1% gel 1.6 g/800 cm ² 12 hr exposure 0.05% gel					
R168-151-7997	Healthy, n=24 0.1% gel 6.8 g, over 20% BSA 10 hr exposure 0.05% gel					
R168-155-8757	Healthy, n=8; IV infusion 15 µg tazarotene/Kg over 20 min.					
	Healthy, n=8; Topical dose 7.82±0.56 g over 20% BSA 12 h exposure, unoccluded					
MULTIPLE DOSE STUDIES						
R168-713-7997	Healthy, n=6 (Japanese) 0.1% gel 1.6 g/800 cm ² 24 hr exposure 0.05% gel					
R168-152-8606	Healthy, n=24 1st dose 0.1% gel, 6.8 g, over 20% BSA 12 hr exposure last dose					
R168-153-8606	Psoriatic patients, n=5 1st dose psoriatic skin: 8-18% BSA 5.23±2.05 g over affected area 12 hr exposure, unoccluded last dose					

IV. SUMMARY OF IN VITRO STUDIES:

A. IN VITRO DRUG PENETRATION, DISTRIBUTION AND METABOLISM IN SKIN

The sponsor did not submit detailed information for the following studies, and only brief summaries were provided.

- a. In vitro percutaneous absorption and drug distribution in human skin:
Using radiolabeled drug, it was determined that approximately 4-5% of the applied dose penetrated into the stratum corneum and 2-4% penetrated into the viable epidermis-dermis layers 24 hours after topical application to freshly excised human skin or human cadaver skin. Drug penetration across the skin and into the receptor fluid was less than 1% of the dose over 24 hours under the study conditions.
- b. Comparison of two formulations: The 2 gel formulations (8606X-14C and 7997X-14C) used in the PK studies were shown to give similar results in skin penetration using human cadaver skin.
- c. Metabolism of tazarotene in human skin:
Approximately 1/3 of the radiolabeled drug was metabolized to the active metabolite (tazarotenic acid) upon penetration across the human skin in vitro.

B. METABOLISM OF TAZAROTENE IN HUMAN BLOOD/PLASMA

Regarding the metabolism of tazarotene, 3 in vitro studies were submitted:

- a. In Phase 1 PK studies, tazarotene was detected in the blood of Japanese subjects but not in the plasma of Caucasian subjects. This study was conducted to investigate the possible difference in the blood/plasma esterase activities between the two races. The study indicated no difference in esterase activities between the two races.
- b. One study was performed in an attempt to pinpoint the esterase responsible for the hydrolysis of tazarotene. In the study, esterase inhibitors were incubated with tazarotene and the results indicated that paraoxon-inhibitable esterases are involved in metabolizing tazarotene in human blood at least in vitro.
- c. The major metabolites found in human stool were more polar than all the identified metabolites. An attempt was made to identify a major polar metabolite using The technique was able to identify the compound as an oxygenated derivative of the active metabolite (AGN 190299), but was unable to confirm the position of the oxygen.

C. OTHER STUDIES:

The following numbers were given without detailed information on the studies.

Blood-to-plasma concentration ratio of the active metabolite:

Plasma protein binding of the active metabolite: about % at a metabolite concentration of ng/mL.

V. ANALYTICAL METHODS:

Throughout the development, various assay methods were used. Method validation data were submitted and are considered satisfactory.

Assay of plasma samples:

VI. COMMENTS:

A. General comments:

1. Two PK studies and several clinical trials used gels manufactured by the new process (aqueous to nonaqueous phase addition). Therefore, there is no need to request an in vitro drug release test to compare the two manufacturing processes for the product.
2. 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. The sponsor provided stability data in plasma samples containing tazarotene in higher concentrations.
3. 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. It is noted that gauze pads wetted with isopropanol were used for skin wash. Does the use of isopropanol change the drug distribution in skin? Furthermore, 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.
4. Results from therapeutic drug level monitoring in Phase 3 clinical trials showed that plasma concentrations were mostly below 1 ng/mL and the highest concentration found was 6.1 ng/mL. There was no correlation between the dosing area (and presumably the dose) and

plasma metabolite concentration. Nor was there a correlation between the blood sampling time (in relation to the dose application time) and plasma metabolite concentration. It is noted that the actual dose for each patient was not known in these clinical trials. However, in a PK study (R168-153-8606) in psoriatic patients, again no correlation between the dosing area (or the dose) and plasma metabolite concentration was found, indicating the skin condition greatly influence the percutaneous absorption.

5. In the multiple dose PK study, much higher plasma concentrations (C_{max} : ng/mL) of the active metabolite were observed upon repeated dosing. Some accumulation can occur due to the elimination half-life. Additionally, the concentration in the skin may take some time to reach steady state. Most of all, the drug may modify the skin and change the percutaneous absorption. The findings of this study has been communicated to the Medical Officer, Dr. Ko.

6. Brief summaries of some in vitro studies were provided. The sponsor should be advised that detailed reports for the studies are expected..

7. The sponsor is encouraged to develop an in vitro drug release test method and test specifications for the gel formulations.

8. Only one female subject was included in one out of 8 PK studies even though the sponsor indicated the drug as used topically was not teratogenic based on nonclinical findings.

B. Labeling comments:

1. Since repeated dosing resulted in greater systemic absorption when compared to that for a single dose, each study cited in the labeling should be labeled as a single dose or multiple dose study. The number of subjects in each study should also be indicated.

2. The compound (tazarotene or metabolite) associated with the plasma concentrations given in the labeling should be specified.

3. The exposure time (e.g. 10 hrs) to topical dose should be indicated for each study given in the labeling since it can affect the quantity absorbed into the systemic circulation.

4. Much higher C_{max} and AUC of tazarotene and its active metabolite were observed upon repeated dosing in psoriatic patients (Study R168-153-8606). These findings should be incorporated into the labeling.

5. We recommend that the labeling read as follows:

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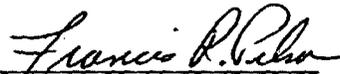
VII. RECOMMENDATION:

From the biopharmaceutics standpoint, the application is acceptable. The labeling should be revised accordingly. Please communicate General Comments #2, 3, 6, 7 and 8, and all Labeling Comments to the sponsor.



Sue-Chih Lee, Ph.D.
Pharmacokinetics Evaluation Branch III

RD/FT Initialed by Frank Pelsor, Pharm.D.



Biopharm Day (Date: 3/18/96; Attendees: Drs. Fleischer, ML Chen, Mehta, Shah, Pelsor, Wang and Lee)

cc: NDA 20-600, HFD-540 (2 copies), HFD-880 (Fleischer, Pelsor, Bashaw, Lee), HFD-860 (Malinowski), Chron, Drug File (Clarence Bott, HFD-870, PKLN 13B31), Reviewer, HFD-205 (FOI), HFD-340 (Viswanathan)

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APPENDIX I: IN VIVO PERCUTANEOUS ABSORPTION/PK STUDIES

1) Study R168-712-7997:

INVESTIGATION ON SAFETY AND PHARMACOKINETICS BY SINGLE TOPICAL APPLICATION (Volumes 1.69 & 1.71)

INVESTIGATOR AND LOCATION:

OBJECTIVES:

To assess safety and pharmacokinetics of tazarotene gel by single topical administration in healthy (Japanese) volunteers.

FORMULATION:

The study used three strengths (0.01%, 0.05% and 0.1%) of gel formulations, but the 0.01% gel was not included in the pharmacokinetic evaluations.

A: 0.1% gel (formulation no. 7997x)

B: 0.05% gel (formulation no. 8225x; with 5% overage of the active)

STUDY DESIGN:

This is a one period, open label, parallel group, single topical application study. Eighteen healthy adult male subjects participated in the study (age: 20-24 yrs., wt: 55-75 Kg; Table 1). Each gel formulation was applied to the back of each of 6 subjects for 12 hours. The dose was 1.6 g of gel per 800 cm² which is equivalent to approximately 13 and 25 µg/kg for the 0.05 and 0.1% gels, respectively.

Sample collections -

Blood samples: Pre-dose, 1, 2, 4, 8, 10, 12, 13, 14, 15, 16, 24, 36, and 48 hours

Urine samples: 0-4, 4-8, 8-12, 12-16, 16-24, 24-36, and 36-48 hours after dosing.

ASSAY:

DATA ANALYSIS:

Blood samples:

Due to paucity of quantifiable concentrations in blood, only C_{max} and T_{max} were estimated.

Drug concentrations below quantitation limit were set to one-half the quantifiable limit for calculations of the mean and standard deviation. However, if less than half of the subjects had quantifiable blood concentrations, the mean C_{max} and T_{max} values were not calculated.

Urine samples:

Urinary excretion rate was determined from urine drug concentration and urine volume. Terminal phase $t_{1/2}$ for urinary excretion rate-time profiles was calculated. For recovery calculations as the % of dose, the mass of each compound was adjusted for their equivalent molecular weight. If more than half of the values for a given set of data were below then no further analysis was carried out. When BLQ values were used, the drug concentration was set to one-half the quantifiable limit.

RESULTS:

Blood Sample Results:

At the low dose (0.05% gel), two subjects had detectable tazarotene concentrations (4 out of 84 total samples) and the highest value was about ng/mL. Three out of 6 subjects showed the free acid metabolite in their blood, and the highest concentration was ng/mL.

At the high dose (0.1% gel), all 6 subjects had detectable blood concentration of tazarotene. However, even two pre-dose samples had detectable tazarotene concentrations. All samples had concentrations less than ng/mL except one ng/mL). Four out of 6 subjects had detectable free acid metabolite in their blood. All samples had concentrations less than ng/mL except one sample ng/mL). The mean C_{max} was 0.09 ± 0.12 ng/mL for tazarotene and 0.05 ± 0.05 ng/mL for the free acid metabolite.

Urine Sample Results:

At a limit of quantitation of 1 ng/mL, no parent compound or metabolite 1 (free acid) or 2 (sulfoxide of the parent compound) were detected in any of the urine samples. Only metabolite 3 (AGN 190844, sulfoxide of the free acid) was found in most of the urine samples. The mean recovery, as metabolite 3, in the urine was $1.2 \pm 1.2\%$ and $0.27 \pm 0.09\%$ of dose after 0.05% and 0.1% tazarotene gel treatment, respectively. The terminal phase $t_{1/2}$ obtained from the urinary excretion data was about 10 hours. The urinary excretion rate were highly variable among individuals. The sponsor explained that this may be due to the low and varied systemic absorption through the skin. Alternatively, the excretion of metabolite 3 could be pH-dependent.

Comments:

1. In this study, urine data points do not appear to be sufficient for determining the terminal half life of the active metabolite.
2. For the urine data, the sponsor provided the urine sample concentrations, the individual urinary excretion rate vs. time plots and the mean %dose excreted in the urine within the 48-hour collection period. The amount excreted in the urine for each collection period was not indicated.

Table 1. Japanese subject and dosing data for study R168-712-7997.

SUBJECT NUMBER	SUBJECT INITIALS	SEX	AGE (years)	HEIGHT (cm)	WEIGHT (kg)	TEST DRUG	DOSE (µg AGN 190168/kg body weight)
		Male				0.05% Gel	1.6g/800cm ² /12h
		Male				0.05% Gel	1.6g/800cm ² /12h
		Male				0.05% Gel	1.6g/800cm ² /12h
		Male				0.05% Gel	1.6g/800cm ² /12h
		Male				0.05% Gel	1.6g/800cm ² /12h
		Male				0.05% Gel	1.6g/800cm ² /12h
Mean ± SD			22 ± 1	174 ± 3	62 ± 6		13 ± 1
		Male				0.1% Gel	1.6g/800cm ² /12h
		Male				0.1% Gel	1.6g/800cm ² /12h
		Male				0.1% Gel	1.6g/800cm ² /12h
		Male				0.1% Gel	1.6g/800cm ² /12h
		Male				0.1% Gel	1.6g/800cm ² /12h
		Male				0.1% Gel	1.6g/800cm ² /12h
Mean ± SD			22 ± 1	170 ± 6	64 ± 7		25 ± 3

Table 2: Tazarotene Concentrations (ng/mL) in Human Whole Blood Specimens - 0.1% Gel

Time (Hour)	Subject#
Pre-dose	
1	
2	
4	
8	
10	
12	
13	
14	
15	
16	
24	
36	
48	

Table 3: AGN 190299 Concentrations (ng/mL) in Human Whole Blood Specimens - 0.1% Gel

Time (Hour)	Subject#
Pre-dose	
1	
2	
4	
8	
10	
12	
13	
14	
15	
16	
24	
36	

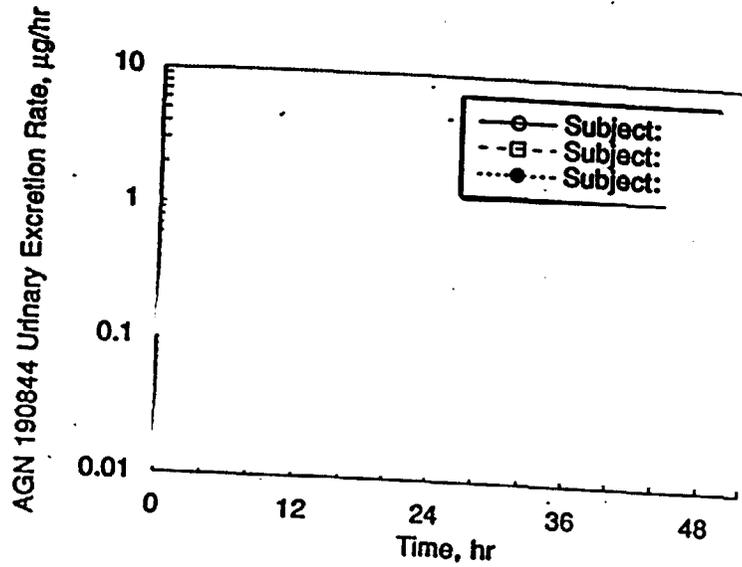


Figure 1. Urinary AGN 190844 excretion rate versus time profile following a single topical dose of a 0.05% AGN 190168 gel to Japanese subjects.

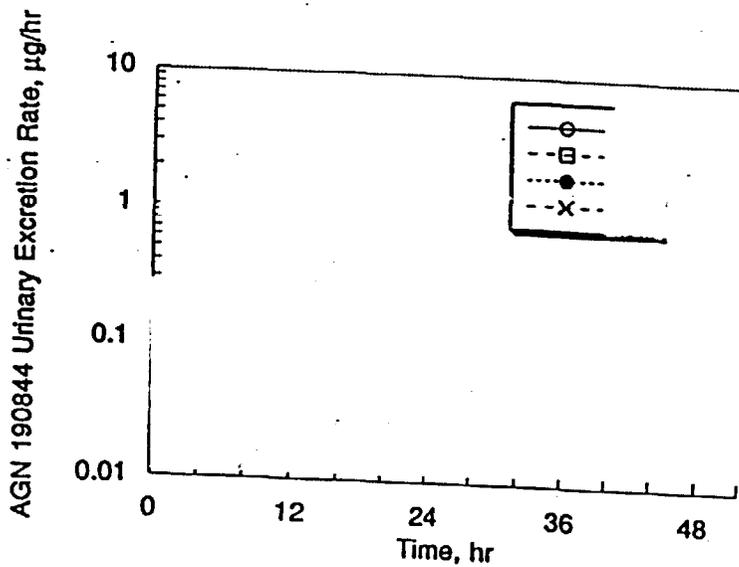


Figure 2. Urinary AGN 190844 excretion rate versus time profile following a single topical dose of a 0.1% AGN 190168 gel to Japanese subjects.

2) Study R168-713-7997 (healthy subjects)

INVESTIGATION ON SAFETY AND PHARMACOKINETICS BY MULTIPLE TOPICAL APPLICATION
(Vol. 1.69 & 1.71)

INVESTIGATOR AND LOCATION:

OBJECTIVES:

To assess safety and pharmacokinetics of tazarotene gel after multiple topical administrations in healthy (Japanese) volunteers.

FORMULATION:

A: 0.1% gel (formulation no. 7997x)

B: 0.05% gel (formulation no. 8225x; with 5% overage of the active)

Formulation contained trolamine instead of tromethamine; Nonaqueous to aqueous phase addition process used.

STUDY DESIGN:

This is a randomized, one period, open label, parallel group, multiple topical application study. Twelve healthy adult male subjects participated in the study (age: 20-25 yrs., wt: 55-76 Kg; Table 1). Each gel formulation was applied once daily to the back of each of 6 subjects for 24 hours. The 0.05% gel was applied for 7 days and the 0.1% gel for 5 days. The dose was 1.6 g of gel per 800 cm² which is equivalent to approximately 13 and 27 µg/kg/day for the 0.05 and 0.1% gels, respectively.

Sample collections -

Blood samples:

<u>0.05% gel</u>	<u>0.1% gel</u>	<u>Sampling time</u>
Day 1	Day 1	Pre-dose, and 2, 6 and 12 hours post-dose
Days 2-6	Days 2-4	0 and 12 hours post-dose
Day 7	Day 5	0, 2, 6 and 12 hours
Day 8	Day 6	0, 1, 2, 4, 6, 12, 24, 36 and 48 hrs. and 1 wk after last treatment

Urine samples:

<u>0.05% gel</u>	<u>0.1% gel</u>	<u>Sampling time</u>
Day 1	Day 1	0-6, 6-12, and 12-24 hrs. post-dose
Days 2-6	Days 2-4	0-24 hrs. post-dose
Day 7	Day 5	0-6, 6-12, and 12-24 hrs.
Day 8	Day 6	0-6, 6-12, 12-24, 24-36 and 36-48 hrs.

ASSAY:

DATA ANALYSIS:

Due to paucity of quantifiable concentrations in blood, only C_{max} and T_{max} were estimated. Drug concentrations below quantitation limit were set to one-half the quantifiable limit for calculations of the mean and standard deviation. However, if less than half of the subjects had quantifiable blood concentrations, the mean C_{max} and T_{max} values were not calculated.

Urinary excretion rate was determined from urine drug concentration and urine volume. Terminal phase t_{1/2} for urinary excretion rate-time profiles was calculated. For recovery calculations as the % of dose, the mass of each compound was adjusted for their equivalent molecular weight. If more than half of the values for a given set of data were below LOQ, then no further analysis was carried out. When BLQ values were used, the drug concentration was set to one-half the quantifiable limit.

RESULTS:

Blood sample results:

At low dose (0.05% gel), all 6 subjects gave quantifiable concentrations of tazarotene upon repeated dosing. The metabolite concentrations in one subject could not be determined due to assay difficulties. Three of the remaining 5 subjects showed some metabolite in their blood.

At the high dose (0.1% gel), all subjects had 4 or less samples (out of 24 samples) with detectable blood concentrations of tazarotene. For the metabolite, data for one subject was lost due to unacceptable QC sample results. Three of the remaining 5 subjects showed metabolite concentrations in their blood. The mean C_{max} was 0.11 ± 0.02 ng/mL for tazarotene and 0.19 ± 0.20 ng/mL for the free acid metabolite.

One week after the termination of the dose application of the 0.05% gel, only Subject had detectable metabolite in his blood. In the high dose group, only Subject had detectable drug in his blood.

Urine sample results:

At a limit of quantitation of ng/mL, no parent compound or metabolite 1 (free acid) or 2 (sulfoxide of the parent compound) were detected in any of the urine samples. Only metabolite 3 (AGN190844, sulfoxide of the free acid) was found in most of the urine samples. The mean recovery, as metabolite 3, in the urine was 0.64 ± 0.34% and 0.28 ± 0.14% of dose after 0.05% and 0.1% tazarotene gel treatment, respectively. The urinary excretion rate were highly variable among individuals treated with 0.1% gel. The terminal phase t_{1/2} obtained from the urinary excretion data was 15-30 hours.

Comment: For the urine data, the sponsor provided the urine concentration for each urine sample collected and the individual urinary excretion rate vs. time plots for the samples collected 24-72 hours after last dose. Also provided was the mean %dose excreted in the urine but the sponsor did not explain how it was calculated.

Table 1. Japanese subject and dosing data for study R168-713-7997.

SUBJECT NUMBER	SUBJECT INITIALS	SEX	AGE (years)	HEIGHT (cm)	WEIGHT (kg)	TEST DRUG	DOSE	
							(Amount of gel/area/dosing period)	(µg AGN 190168/kg body weight)
		Male				0.05% Gel	1.6g/800cm ² /24h x 7 days	
		Male				0.05% Gel	1.6g/800cm ² /24h x 7 days	
		Male				0.05% Gel	1.6g/800cm ² /24h x 7 days	
		Male				0.05% Gel	1.6g/800cm ² /24h x 7 days	
		Male				0.05% Gel	1.6g/800cm ² /24h x 7 days	
		Male				0.05% Gel	1.6g/800cm ² /24h x 7 days	
Mean ± SD			22 ± 1	174 ± 8	64 ± 8			13 ± 2
		Male				0.1% Gel	1.6g/800cm ² /24h x 5 days	
		Male				0.1% Gel	1.6g/800cm ² /24h x 5 days	
		Male				0.1% Gel	1.6g/800cm ² /24h x 5 days	
		Male				0.1% Gel	1.6g/800cm ² /24h x 5 days	
		Male				0.1% Gel	1.6g/800cm ² /24h x 5 days	
		Male				0.1% Gel	1.6g/800cm ² /24h x 5 days	
Mean ± SD			23 ± 2	173 ± 6	60 ± 4			27 ± 2

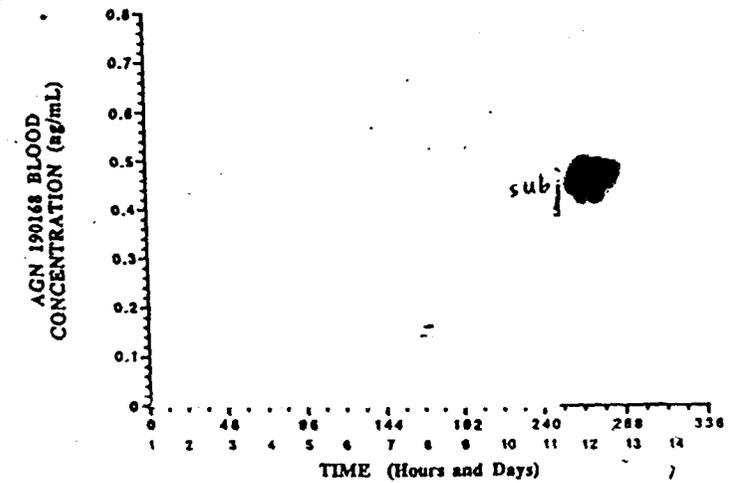
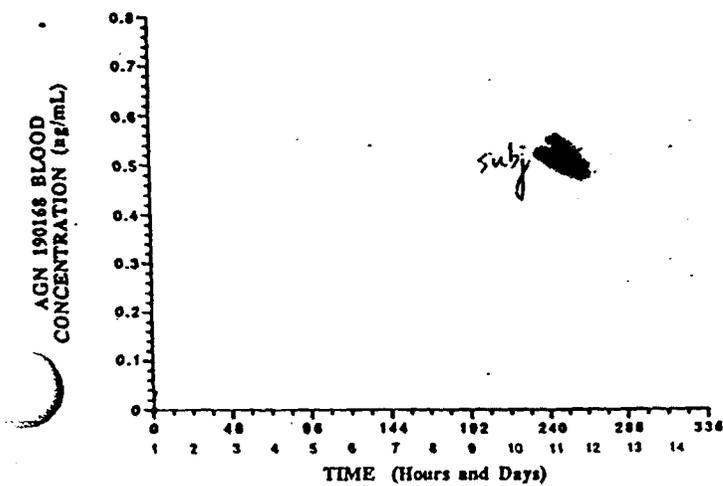
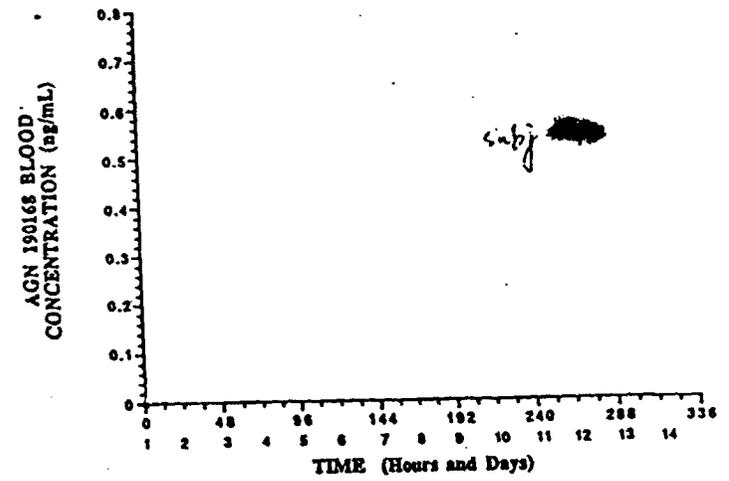
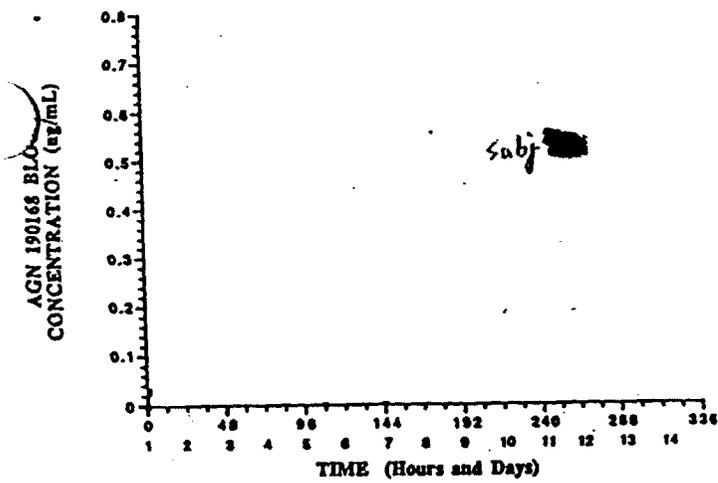
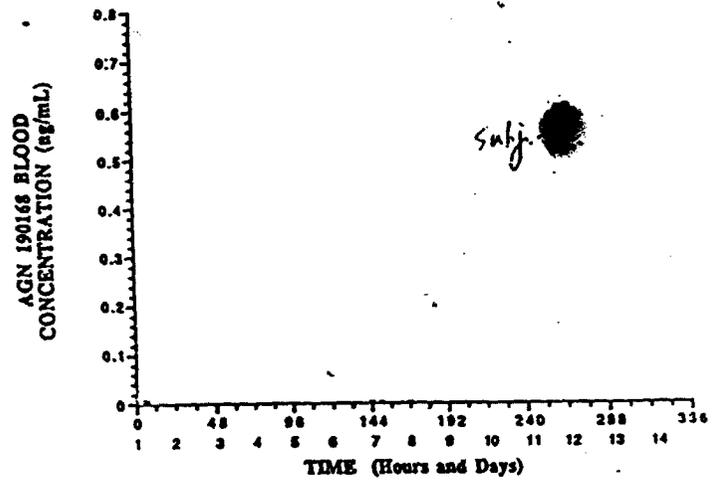
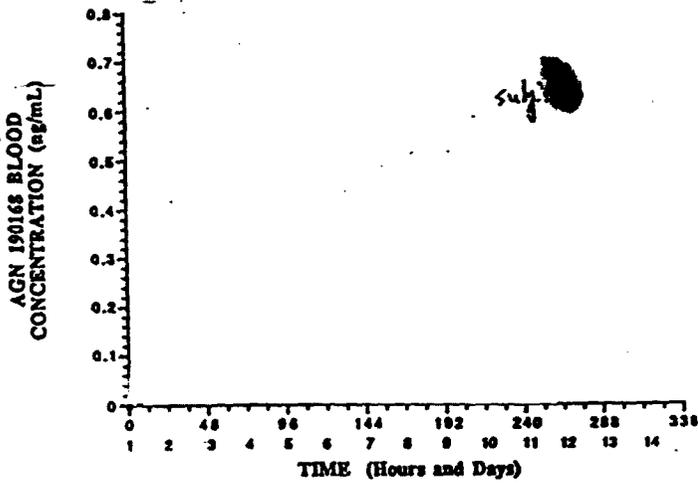
Table 2: Tazarotene Concentrations (ng/mL) in Human Whole Blood Specimens Following Multiple Dosing of 0.1% Gel

Day	Time (Hour)	Subj 1	Subj 2	Subj 3	Subj 4	Subj 5	Subj 6
1	8 AM (Pre-dose)						
1	10 AM						
1	2 PM						
1	8 PM						
2	8 AM						
2	8 PM						
3	8 AM						
3	8 PM						
4	8 AM						
4	8 PM						
5	8 AM						
5	10 AM						
5	2 PM						
5	8 PM						
6	8 AM						
6	9 AM						
6	10 AM						
6	12 PM						
6	2 PM						
6	8 PM						
7	8 AM						
7	8 PM						
8	8 AM						
12	8 AM						

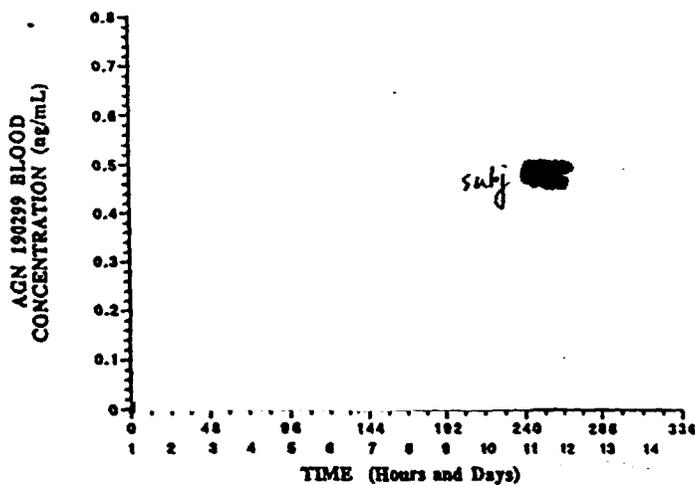
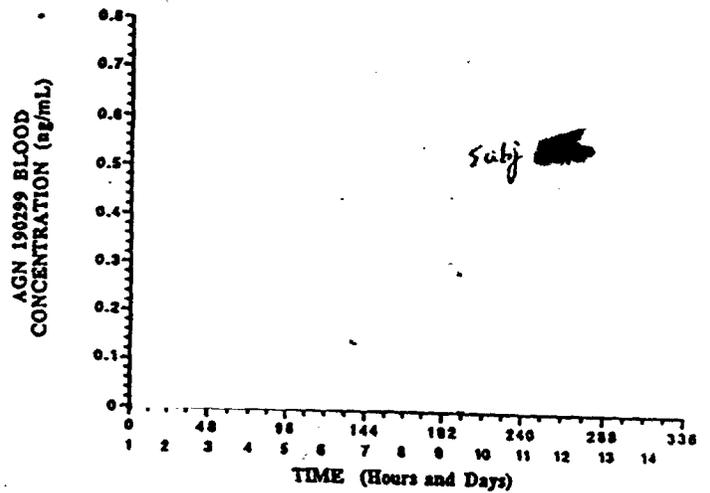
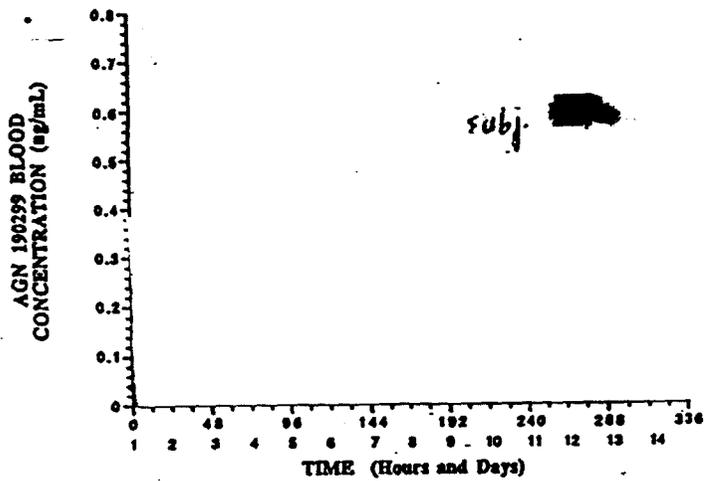
Table 3: AGN190299 (Metabolite) Concentrations (ng/mL) in Human Whole Blood Specimens Following Multiple Dosing of 0.1% Gel

Day	Time (Hour)	Subj 1	Subj 2	Subj 3	Subj 4	Subj 5	Subj 6
1	8 AM (Pre-dose)						
1	10 AM						
1	2 PM						
1	8 PM						
2	8 AM						
2	8 PM						
3	8 AM						
3	8 PM						
4	8 AM						
4	8 PM						
5	8 AM						
5	10 AM						
5	2 PM						
5	8 PM						
6	8 AM						
6	9 AM						
6	10 AM						
6	12 PM						
6	2 PM						
6	8 PM						
7	8 AM						
7	8 PM						
8	8 AM						
12	8 AM						

Figure 1:
Tazarotene Blood Concentration-Time Profiles Following Multiple Dosing of a 0.05% Gel



**Figure 2: AGN190299 (Metabolite) Blood Concentration-Time Profiles
Following Multiple Dosing of a 0.05% Gel**



Note: Subject [redacted] had no detectable metabolite concentrations.
Subject [redacted] had only one sample with detectable metabolite concentration (0.0499 ng/mL).
No results could be reported for Subject [redacted] due to assay difficulties.

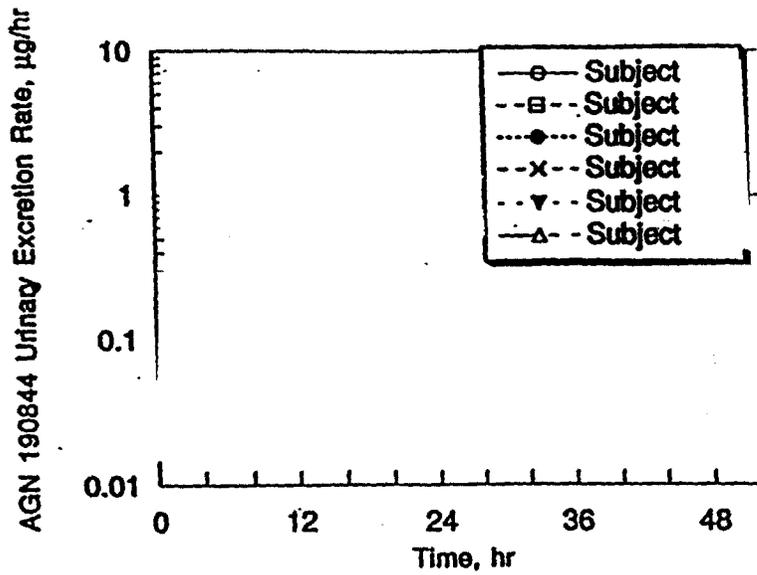


Figure 2. Urinary AGN 190844 excretion rate versus time profile following multiple topical doses of a 0.05% AGN 190168 gel to Japanese subjects.

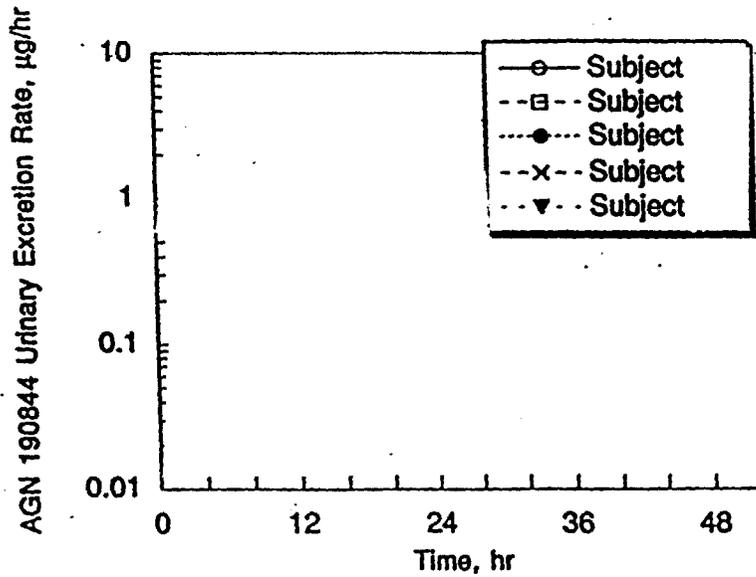


Figure 3. Urinary AGN 190844 excretion rate versus time profile following multiple topical doses of a 0.1% AGN 190168 gel to Japanese subjects.

3) Study R168-151-7997 (healthy subjects)

A STUDY TO DETERMINE THE PLASMA CONCENTRATION TIME PROFILE FOLLOWING SEPARATE TOPICAL ADMINISTRATION OF TWO CONCENTRATIONS OF AGN 190168 (0.1% AND 0.05%) GELS IN HEALTHY MALE VOLUNTEERS
(Vol. 1.70)

INVESTIGATOR AND LOCATION:

OBJECTIVES:

To evaluate the plasma concentration-time profile of two concentrations (0.1% and 0.05%) of a gel formulation containing tazarotene following topical application to approximately 20% of the body surface area of 24 healthy male adult volunteers.

FORMULATION:

A: 0.1% gel (formulation no. 7997x)

B: 0.05% gel (formulation no. 8225x; with 5% overage of the active)

STUDY DESIGN:

Design: This was a single-center, open-label, randomized, single-dose, two-way crossover study with a washout period of at least 14 days. Twenty-four male subjects (age: 22.2 ± 2.5 yrs., wt.: 172.5 ± 15.4 lb) entered and completed the study.

Dose application: Approximately 6.8 g of gel (2 mg/cm^2) was applied to 20% of the total body surface area (face, neck, chest, abdomen, frontal thigh). This dose delivered approximately 6.8 mg (or 0.1 mg/Kg) and 3.4 mg (or 0.05 mg/Kg) of tazarotene for the 0.1% and 0.05% gel formulations, respectively. The application site was not covered by clothing. The medication was removed 10 hours after application and the area was thoroughly washed with soap and water.

Samples: Blood samples were collected at pre-dose, 2, 4, 6, 8, 10, 10.5, 11, 12, 14, 16, 20, 24, 36, 48, and 72 hours after each drug application.

ASSAY:

DATA ANALYSIS:

Analysis of Variance procedures were performed on pharmacokinetic parameters (AUC_{24} , AUC_{TLDC} , AUC_{INF} , C_{MAX} , T_{MAX} , Ratio of parameters, K_{EL} , $T_{1/2}$). For calculations of AUC, values of 0.025 ng/mL were assigned to the below limit of quantitation values which occurred immediately after the last quantifiable concentration. ANOVA procedures were also

performed on log-transformed data to obtain geometric means and calculate a 90% geometric confidence interval using a two one-sided t-test on these means.

RESULTS:

Plasma concentrations of the parent compound were below the _____ ng/mL following dosing with either the 0.1% or 0.05% gel. The mean plasma concentration of the free acid metabolite peaked at 14.2 hours after dosing with the 0.1% gel ($C_{MAX} = 0.47 \pm 0.25$ ng/mL) and at 14.8 hours after dosing with the 0.05% gel ($C_{MAX} = 0.33 \pm 0.17$ ng/mL). The highest plasma metabolite concentrations observed was about _____ ng/mL for the _____ % and _____ % gel, respectively. Mean plasma concentrations of the metabolite fell after dose removal with a $T_{1/2}$ of 15.0 ± 7.9 hours for the 0.1% gel and 16.9 ± 6.4 hours for the 0.05% gel.

There was no sequence effect in this study and, except for T_{MAX} , there was no period effect. The mean T_{max} was 16.1 ± 4.2 hours for Period I and 12.9 ± 1.8 hours for Period II. There were statistically significant differences between the 0.1% gel and the 0.05% gel for mean AUC_{24} , AUC_{TLDC} , AUC_{INF} and C_{MAX} . The amount of drug absorbed into the bloodstream as measured by AUC increased approximately 40% for the 0.1% gel (14.6 ± 6.8 ng/mL) when compared to that for the 0.05% gel (10.6 ± 3.8 ng/mL).

No serious systemic adverse events were reported. With the exception of one mild case of light-headedness (considered as unlikely to be related to the study medication), all other adverse events were limited to skin irritation and/or pruritus at the application sites (71% of incidences for the 0.1% gel and 63% for the 0.05% gel). The higher dose (0.1% gel) resulted in a higher incidence of adverse events.

Comments:

1. There was period effect for T_{max} ($p = 0.001$). Skin might be more permeable in Period II than in Period I. However, there was no statistically significant differences in C_{max} or AUC between the 2 periods.
2. Many volunteers (54% for 0.1% gel) experienced severe itching/burning. This adverse effect should be evaluated by the medical officer.

Table I:

• Summary of mean (\pm SD) pharmacokinetic parameters for AGN 190299 are as follows (n = 24, except where noted):

Pharmacokinetic Parameters	0.1% Gel*	0.05% Gel**	p-value
AUC ₀₋₂₄ (ng•h/ml)	6.09 \pm 3.23	4.36 \pm 2.17	0.0006
[range]	[1.84 - 12.4]	[1.61 - 8.91]	
AUC _{0-TLDC} (ng•h/ml)	9.71 \pm 6.16	7.18 \pm 3.60	0.0097
[range]	[1.84 - 23.8]	[1.61 - 16.2]	
AUC _{INF} (ng•h/ml)	14.6 \pm 6.83†	10.6 \pm 3.80††	0.0095
[range]	[5.60 - 30.8]	[5.90 - 19.2]	
C _{MAX} (ng/ml)	0.47 \pm 0.25	0.33 \pm 0.17	0.0004
[range]	[0.14 - 0.96]	[0.11 - 0.70]	
T _{MAX} (h)	14.2 \pm 3.74	14.8 \pm 3.46	0.5136
[range]	[10.5 - 24.0]	[10.0 - 24.0]	
K _{EL} (1/h)	0.05 \pm 0.02†	0.04 \pm 0.02††	0.2797
[range]	[0.01 - 0.11]	[0.02 - 0.07]	
T _{1/2} (h) (harmonic mean)	15.0 \pm 7.9†	16.9 \pm 6.4††	0.2759
[range]	[6.60 - 50.5]	[9.48 - 34.8]	

* Approximate total dose of AGN 190168 was 0.1 mg/kg
 ** Approximate total dose of AGN 190168 was 0.05 mg/kg
 † n=20
 †† n=21

Table II:

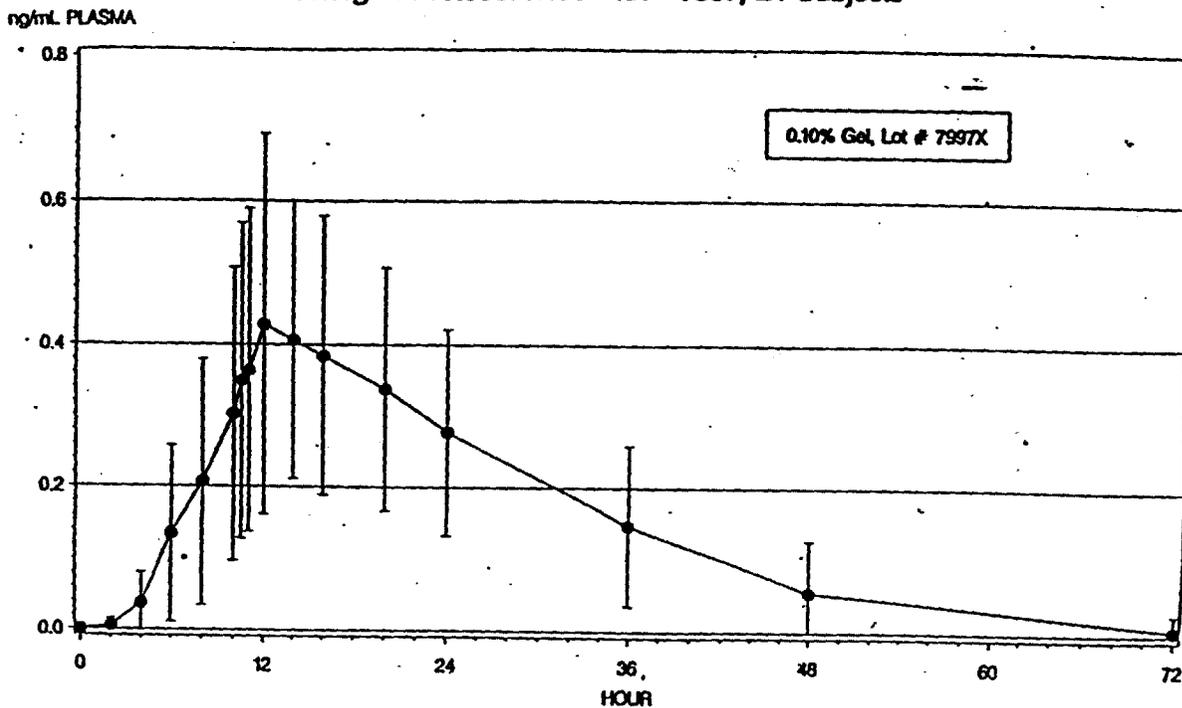
PARAMETER	TEST/REFERENCE (0.1%/0.05%) RATIO	90% CI OR TWO ONE- SIDED t-TESTS
AUC ₀₋₂₄	136	(120; 155)
AUC _{0-TLDC}	127	(108; 150)
AUC _{INF} *	125	(104; 150)
C _{MAX}	139	(122; 158)
T _{MAX}	96	(88; 105)
K _{EL} *	122	(96; 156)
T _{1/2} *	82	(64; 105)

* n = 20

** Log-Transformed data.

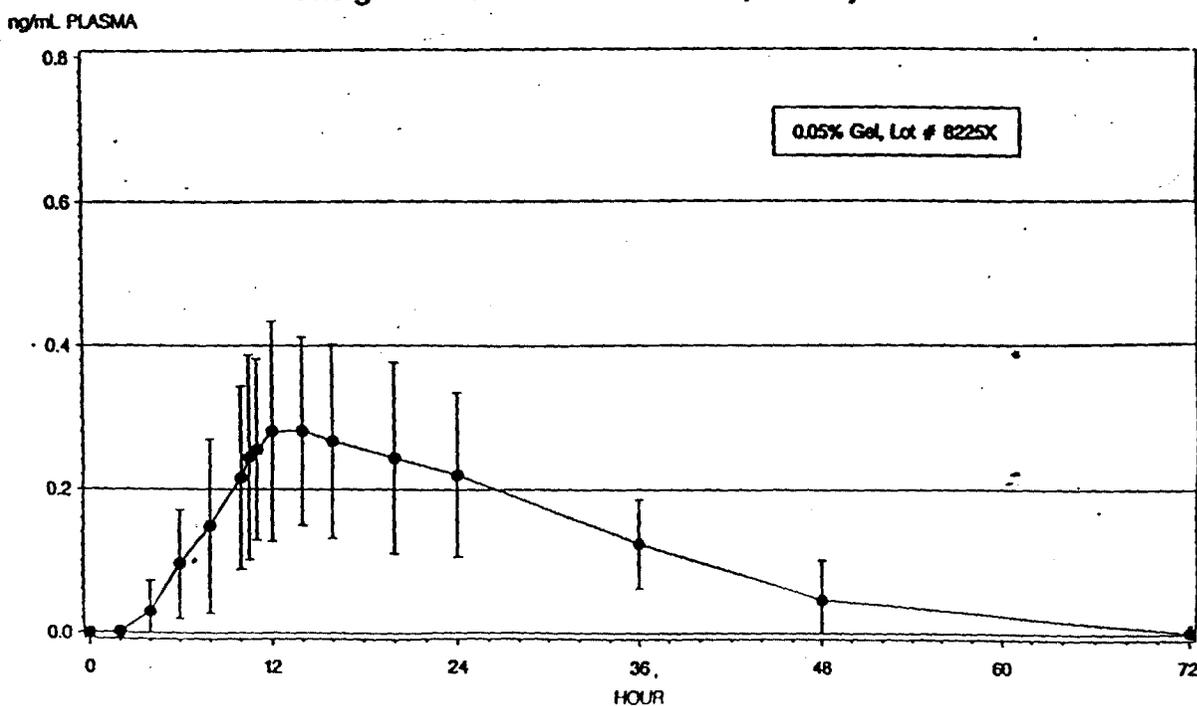
I
FIGURE 1

Mean \pm SD Plasma AGN 190299 Concentration versus Time Allergan Protocol R168-151-7997, 24 Subjects

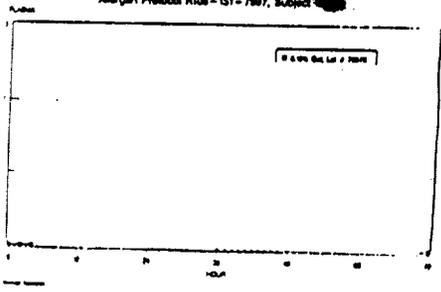


II
FIGURE 2

Mean \pm SD Plasma AGN 190299 Concentration versus Time Allergan Protocol R168-151-7997, 24 Subjects

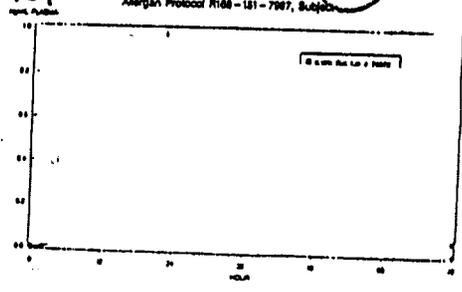


Plasma AGN 190 Concentration versus Time
Allergen Protocol R168-151-7987, Subject [redacted]

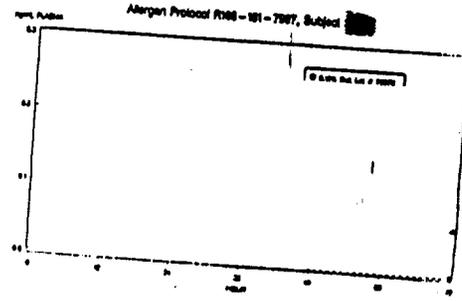


--- : 0.05% Gel

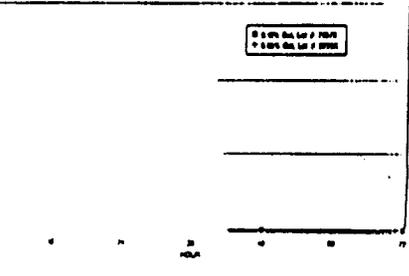
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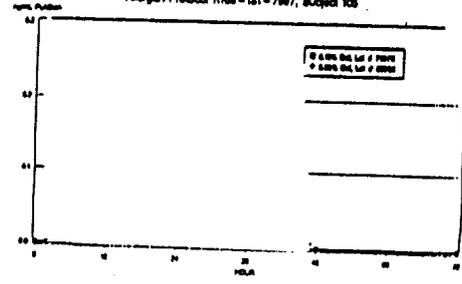
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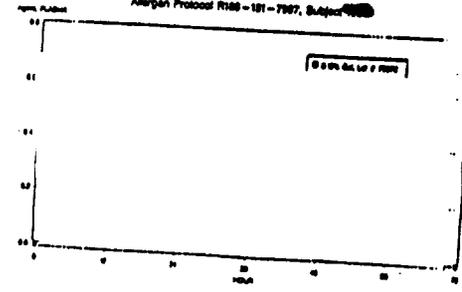
Allergen Protocol R168-151-7987, Subject [redacted]



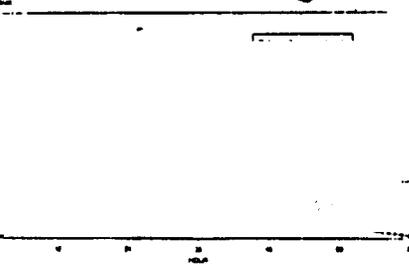
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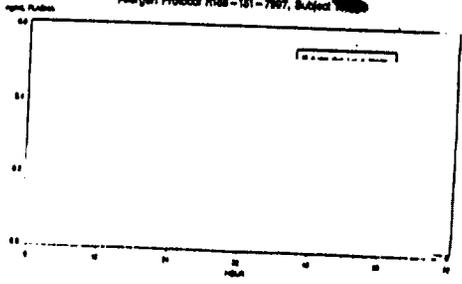
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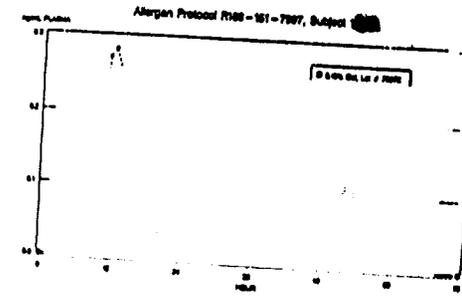
Subject [redacted]



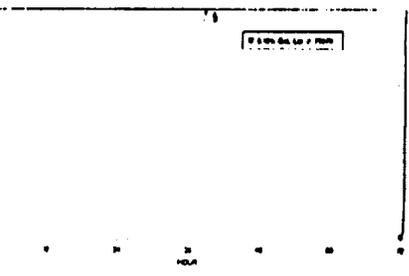
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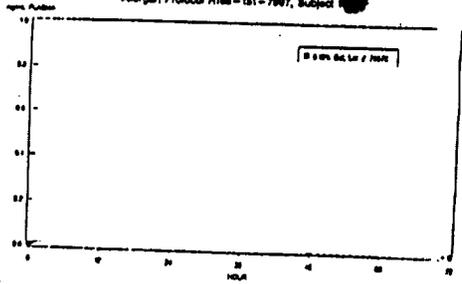
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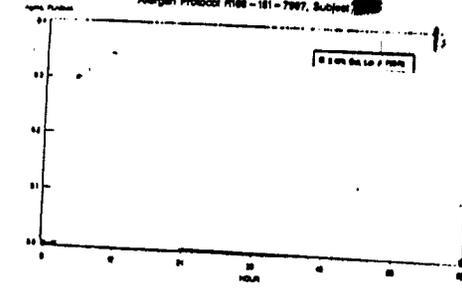
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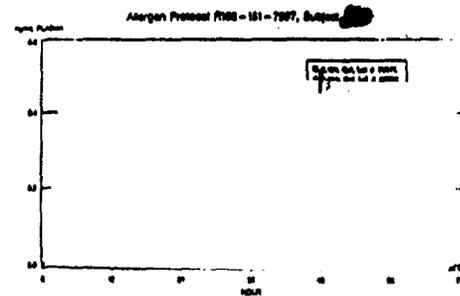
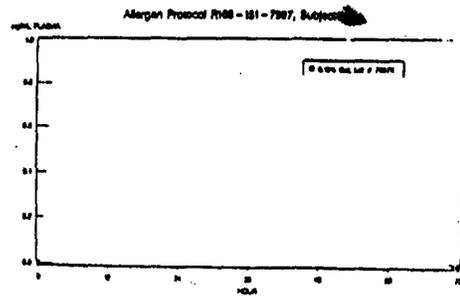
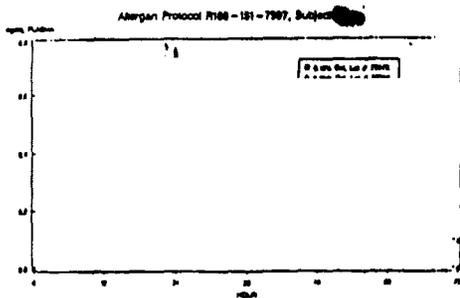
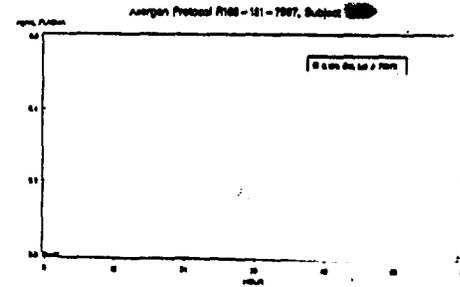
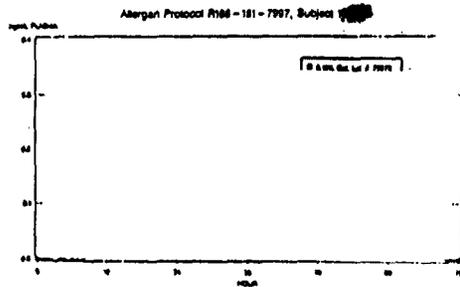
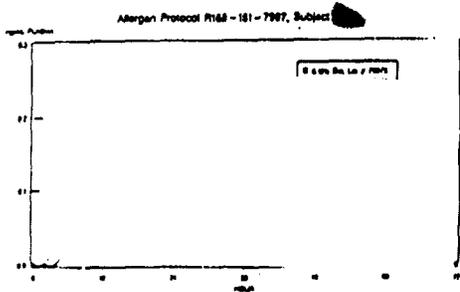
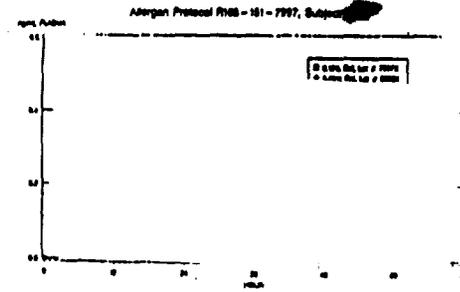
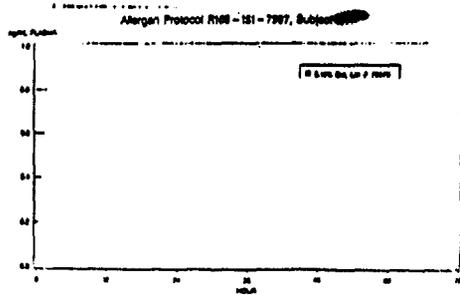
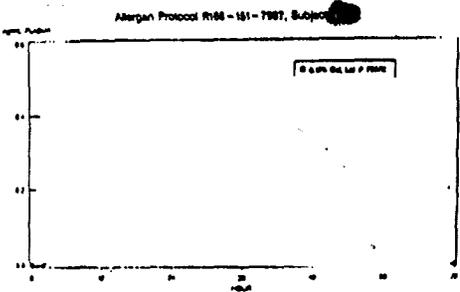
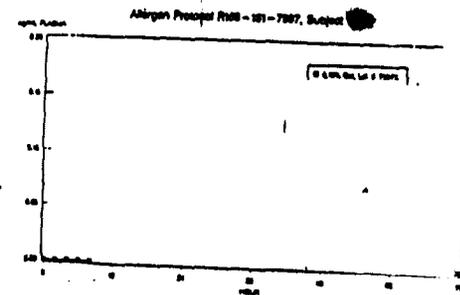
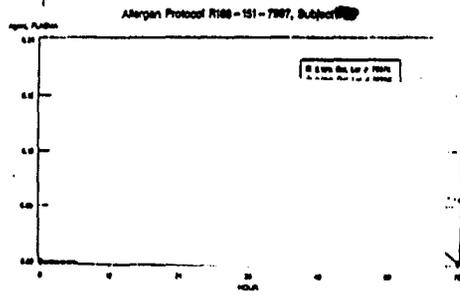
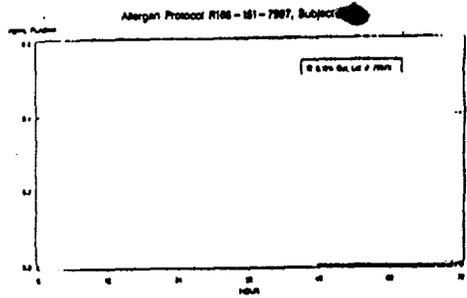


Allergen Protocol R168-151-7987, Subject [redacted]



Allergen Protocol R168-151-7987, Subject [redacted]





4) Study R168-154-8606

**PERCUTANEOUS ABSORPTION AND MASS BALANCE OF ¹⁴C-AGN 190168
FOLLOWING A SINGLE TOPICAL APPLICATION OF ¹⁴C-AGN 190168 0.1% GEL
TO PSORIATICS** (Vol. 1.71, p. 90)

INVESTIGATOR AND LOCATION:

OBJECTIVES:

To determine the extent of percutaneous absorption, mass balance and safety following a single topical application of ¹⁴C-AGN 190168 0.1% gel to lesional skin of psoriatics.

FORMULATION: 8606X-C14D

The specific radioactivity of the gel was $\mu\text{Ci/g}$ and the radiochemical purity was %.

STUDY DESIGN:

Six male subjects (mean age: 50.3 ± 9.4 yrs.; mean wt.: 89 ± 13.6 Kg) with stable plaque psoriasis entered the study. The gel was applied to psoriatic plaques of each patient for 10 hours, excluding the face, scalp and intertriginous areas. An area of psoriasis equal to 5% of the total body surface area was treated. The application dose was targeted at 2 mg/cm^2 . Ten hours after application, the treated areas were wiped thoroughly with gauze pads wetted with isopropanol to remove the residual medication.

SAMPLE COLLECTIONS AND ANALYSIS:

Skin samples:

At 10 h post-dose, the application site was tape-stripped five times after treatment area wash to recover the drug remaining on the skin surface. The area designated for skin biopsy was tape-stripped a further 10-35 times to obtain stratum corneum, then 2 skin biopsies (separated into epidermis and dermis) of 3.0 mm in diameter were collected from the same site. At 10h after dosing and at 24 h intervals, the application site was washed and covered with a non-occlusive dressing. On Study Day 7, the skin was again tape-stripped 5 times. The skin wipe, strip tape and skin biopsies as well as applicator and protective coverings were extracted with solvent (Soluene/Toluene or isopropanol) and analyzed for radioactivity using Liquid Scintillation Counter (LSC). The LOQ of the method was ng-eq/mL or g.

Blood samples: pre-dose and 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36, 48, 60, 72, 120 and 168 hours post-dose.

The 60 hour samples were inadvertently not collected. From each sample, three 0.2 mL aliquots of whole blood were taken, placed into combustion cones and stored at -70°C . The remaining blood was centrifuged and three 0.5 mL aliquots were taken from the plasma for radioactivity analysis using ng-eq/mL . The remaining plasma was stored at -70°C .

Urine samples: pre-dose (4 hour interval prior to dosing), and at 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-16, 16-24, 24-36, 36-48 hours post-dose for Days 0 and 1. Urine was collected at 24 hour intervals for Days 2 to 7.

The total volume in each sample was measured and then three 1.0 mL aliquots were taken for radioactivity analysis using γ -counter. The remaining urine was stored at -70°C .

Feces samples: Collected as the subjects provided and stored at -70°C until lyophilized.

DATA ANALYSIS:

Concentrations of radioactivity in samples were calculated from dpm values and tissue volume, and were expressed as pg-eq/mL using the specific activity of the gel formulation. The half life of urinary or fecal excretion was calculated by linear regression of the logarithmic mean excretion rate versus midpoint of the collection time.

RESULTS:

The subjects had a mean body surface area of $2.08 \pm 0.105 \text{ m}^2$ and the mean dose applied to the subjects was $2.26 \pm 0.185 \text{ g gel}$. This is equivalent to a dose of $21.8 \pm 1.08 \text{ mg tazarotene per m}^2$ or $0.026 \pm 0.003 \text{ mg/Kg}$. (See Table 1.)

Radioactivity in the tape strippings of stratum corneum represented $0.39 \pm 0.305\%$ of the dose. When extrapolated to total applied area, $4.54 \pm 3.67\%$ dose was present in the stratum corneum at dose removal. A nearly uniform distribution of radioactivity across the depth of stratum corneum was observed with these patients (Table II).

From punch biopsies of the skin, a mean of $(9.42 \pm 8.70) \times 10^{-5} \%$ and $(6.64 \pm 6.32) \times 10^{-5} \%$ of the dose was recovered from the epidermis and dermis, respectively, which upon extrapolation to the total applied area, yielded a mean of $1.38 \pm 1.28\%$ and $0.97 \pm 0.89\%$ of dose in epidermis and dermis, respectively (extrapolation factor: 15,000x).

The mean urinary excretion rate increased steadily to reach a maximum of $0.0201 \pm 0.0164\%$ dose at 11.3 hr post-dose (about the time of dose removal). Excretion rate then declined over time to reach non-quantifiable levels by the 120-144 hr collection interval. Over the 7-day time period, the mean cumulative amount of radioactivity excreted in the urine was $0.329 \pm 0.228\%$ of the applied dose with most (96.4%) radioactivity excreted in the first 72 hours. The half-life as determined from the mean urinary excretion rate profile was 15.6 h.

The mean fecal excretion rate reached a maximum of $0.0132 \pm 0.0153\%$ Dose at 35 h post-dose. Fecal excretion rate then declined slowly over time. Over the 7-day period, the cumulative amount of radioactivity excreted in feces was $0.426 \pm 0.472\%$ of the applied dose with most (91.3%) of the radioactivity excreted in the first 72 hours. The half life as determined from the fecal excretion rate profile was 17.3 h.

The mean total recovery (mass balance) of radiolabeled material was $101.5 \pm 11.6\%$ of dose, excluding any radioactivity that might still remain in the skin. The mean recovery from the protective coverings and gauze wipes was $96.7 \pm 11.5\%$ on Day 0 and 2.26% on subsequent

days. Mean recovery from the first 5 tape-strippings was $1.44 \pm 0.82\%$ for Day 0 and $0.0065 \pm 0.0101\%$ for Day 7. The results indicate that 10 hours after the dose application, most ($>98\%$) of the applied dose remained on the skin surface. Absorption into systemic circulation was low with less than 1% excreted in urine and feces over 7 days.

Very low radioactivity was observed with all blood samples (<300 pg equivalent/mL) and plasma samples (<500 pg equivalent/mL). For all except one, plasma radioactivity concentrations decreased to non-detectable levels at 16-48 hr post-dose. The mean plasma C_{max} was 111 ± 160 pg-eq/mL at 12.7 hr post-dose.

The systemic adverse event (1 case of diarrhea) was considered unlikely to be related to the subject medication. No report on local side effects was provided.

COMMENTS:

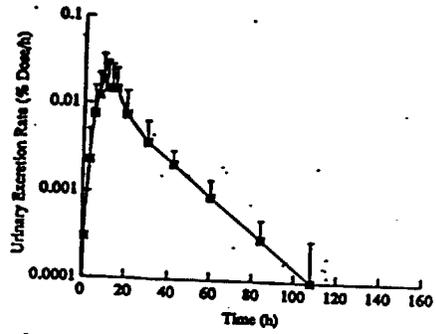
1. For the removal of the applied dose at 10 hours after application, the skin wash was monitored using a Geiger Counter. Any area demonstrating high levels of radioactivity was rewiped with gauze pads until the level of radioactivity was deemed acceptable. The sponsor did not indicate what the acceptable level was and how it was determined. After the skin wash, the drug removed by the first five tape strippings were considered to be drug stayed on the skin surface.
2. The mass balance based on recovery of radioactivity on Day 0 from the skin surface ($96.68\% + 1.44\%$) and in the skin ($4.54\% + 1.38\% + 0.97\%$) amounted to about 105%.
3. On Day 7 post-dose, the quantity of radioactivity remaining in the skin (stratum corneum, epidermis and dermis) was not determined and it was assumed to be zero in mass balance calculations. However, this might not hold true.
4. The study design should have included a multiple dose phase where a hot dose was given as the last dose. With such design, it would have been possible to determine whether there is change in percutaneous absorption upon repeated dosing.

KEY RESULTS

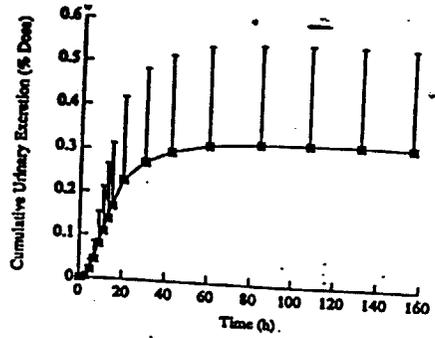
Mean \pm S.D. (n=6) of key results are presented as follows:

Parameter	Result
RECOVERY OF RADIOLABEL	
Skin Surface, Day 0, Entire Treatment Area, by Tape-Strip (% Dose)	1.44 \pm 0.82
Stratum Corneum, Day 0, Biopsy Site Only, by Tape-Strip (% Dose)	0.392 \pm 0.305
Skin Surface, Day 7, Entire Treatment Area, by Tape-Strip (% Dose)	0.0065 \pm 0.0101
Cover and Wipes (% Dose)	98.9
Cumulative Excretion into Urine, 0-168 h (% Dose)	0.329 \pm 0.228
Cumulative Excretion into Feces, 0-168 h (% Dose)	0.426 \pm 0.472
Total Recovery of Radiolabel, 0-168 h (% Dose)	101.5 \pm 11.6
URINE	
Peak Urinary Excretion Rate (% Dose/h)	0.0201 \pm 0.0164
Mid-Point Time of Peak Urinary Excretion Rate (h)	11.3 \pm 3.4
Elim. Rate Constant of Mean Excretion Rate profile (/h)	0.0443
Half-Life of Mean Excretion Rate profile (h)	15.6
FECES	
Peak Fecal Excretion Rate (% Dose/h)	0.0133 \pm 0.0153
Mid-Point Time of Peak Fecal Excretion Rate (h)	35.0 \pm 20.6
Elim. Rate Constant of Mean Excretion Rate profile (/h)	0.0400
Half-Life of Mean Excretion Rate profile (h)	17.3
SKIN	
% Dose in Stratum Corneum, ETA*	4.54 \pm 3.67
% Dose in Epidermis ETA*	1.38 \pm 1.28
% Dose in Dermis ETA*	0.966 \pm 0.886
BLOOD	
Blood Cmax (pg-eq/mL)	90.08 \pm 99.77
Blood tmax (h)	17.3 \pm 15.7
PLASMA	
Plasma Cmax (pg-eq/mL)	111.76 \pm 159.32
Plasma tmax (h)	12.7 \pm 8.7

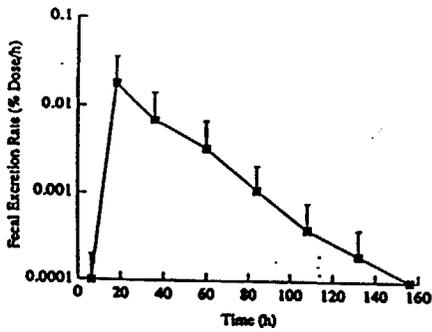
* ETA = Extrapolated to Total Applied Area; samples taken at drug removal



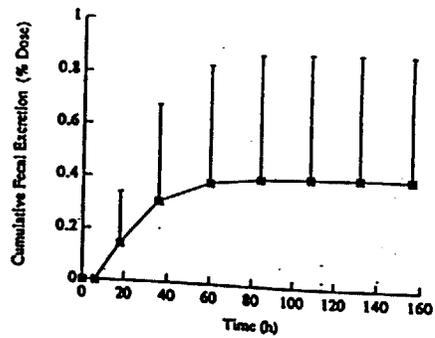
I
 Figure Urinary Excretion Rate versus Time Profile of Total Radioactivity:
 Semi-Logarithmic plot (Mean \pm S.D.)



II
 Figure Cumulative Urinary Excretion versus Time Profile of Total Radioactivity:
 Linear plot (Mean \pm S.D.)



III
 Figure Fecal Excretion Rate versus Time Profile of Total Radioactivity:
 Semi-Logarithmic plot (Mean \pm S.D.)



IV
 Figure Cumulative Fecal Excretion versus Time Profile of Total Radioactivity:
 Linear plot (Mean \pm S.D.)

Table 1. Summary of Drug Dispensed and Calculations of Applied Dose as mg AGN 190168/m² and mg AGN 190168/kg, with Summary Statistics.

Subject ID	Mean		
	Mean	SD	CV%
Cal Dispensed (g)	2.3793	0.1843	8.1743
Specific Activity (μCi/g)			
Total Dispensed (μCi)	192.6	15.74	8.2
Loss Application (μCi)	1.38	0.59	43.01
Total Amount Applied (μCi)	191.2	15.6	8.2
Amount Gel Applied (g)	2.36	0.185	8.3
Total Body Surface Area (sq. m)	2.08	0.103	5.1
Applied Body Surface Area (sq. m)	0.104	0.005	5.1
Dose Applied (mg AGN 190168/m ²)	21.80	1.078	4.9
Dose Applied (mg AGN 190168/kg)	0.726	0.037	10.4

Table 2. % Dose Recovered from Stratum Corneum by Tape Stripping of Biopsied Areas, with Summary Statistics.

Strip No.	Subject ID	Mean		
		Mean	SD	CV%
1		0.0201	0.0111	55.3
2		0.0271	0.0203	111.6
3		0.0267	0.0233	153.3
4		0.0296	0.0248	116.7
5		0.0246	0.0246	136.1
6		0.0210	0.0202	139.0
7		0.0253	0.0226	177.7
8		0.0211	0.0190	162.0
9		0.0244	0.0141	97.6
10		0.0221	0.0111	92.0
11		0.0207	0.0051	56.8
12		0.0294	0.0084	72.5
13		0.0202	0.0084	81.0
14		0.0202	0.0102	103.2
15		0.0200	0.0084	68.2
16		0.0202	0.0097	114.0
17		0.0202	0.0049	83.0
18		0.0201	0.0052	95.2
19		0.0202	0.0051	81.2
20		0.0204	0.0080	92.1
21		0.0204	0.0116	136.5
22		0.0210	0.0092	78.4
23		0.0210	0.0191	226.0
24		0.0274	0.0080	93.7
25		0.0213	0.0125	136.1
26		0.0223	0.0123	100.2
27		0.0229	0.0138	107.1
28		0.0207	0.0083	94.0
29		0.0207	0.0119	129.6
30		0.0270	0.0059	82.8
31		0.0244	MC	MC
32		0.0290	MC	MC
33		0.0231	MC	MC
34		0.0214	MC	MC
35		0.0292	MC	MC
Total % Dose in Stripped Areas		0.3923	0.3047	77.7
Total % Dose in Stratum Corneum		4.3268	3.8092	80.9

MC - Not calculable
 NA - Not available
 ETA - Extrapolated to Total Area

Table 3. Radioactivity Mass Balance, with Summary Statistics

Source	Recovery of Radioactivity (% Dose)		
	Mean	SD	CV%
Skin Surface, Day 0, Entire Treatment Area, by Tape Strip	1.444	0.822	56.96
Stratum Corneum, Day 0, Biopsied Area, by Tape Strip	0.3923	0.305	77.65
Skin Surface, Day 7, Entire Treatment Area, by Tape Strip	0.0065	0.0101	155.32
	1.8423		
Cover and Wipe Day 0	96.08	11.46	11.86
Cover and Wipe Day 1	1.80	0.95	59.30
Cover and Wipe Day 2	0.43	0.27	63.93
Cover and Wipe Day 3	0.09	0.09	103.29
Cover and Wipe Day 4	0.06	0.08	124.52
Cover and Wipe Day 5	0.03	0.03	129.18
Cover and Wipe Day 6	0.02	0.02	121.56
Cover and Wipe Day 7	0.04	0.06	231.23
	96.93		
Urine	0.329	0.228	69.31
Stool	0.426	0.472	110.34
	0.755		
Total Recovered	96.46	97.62	123.87
	91.31	96.51	103.49
	101.53	116.82	117.45

Table 4. Summary of Pharmacokinetic Parameters

Subject ID	Mean		
	Mean	SD	CV%
URINE			
Cumulative Excretion into Urine (% Dose)	0.329	0.228	69.31
Peak Urinary Excretion Rate (% Dose/h)	0.0201	0.0164	81.4
Mid-Point Time of Peak Urinary Excretion Rate (h)	11.3	3.4	30.4
Elim. Rate Constant of Mean Excretion Rate profile (h)	0.0443		
Half-Life of Mean Excretion Rate profile (h)	15.6		
FECES			
Cumulative Excretion into Feces (% Dose)	0.426	0.472	110.8
Peak Fecal Excretion Rate (% Dose/h)	0.0233	0.0153	114.8
Mid-Point Time of Peak Fecal Excretion Rate (h)	35.0	20.4	58.8
Elim. Rate Constant of Mean Excretion Rate profile (h)	0.0400		
Half-Life of Mean Excretion Rate profile (h)	17.3		
BLOOD			
Blood C _{max} (pg-ug/mL)	90.08	99.77	110.8
Blood t _{max} (h)	17.3	15.7	90.8
PLASMA			
Plasma C _{max} (pg-ug/mL)	111.76	159.32	142.3
Plasma t _{max} (h)	12.7	8.7	68.9

5
Table II. % Dose Excreted into the Urine by Time Period, with Summary Statistics.

Time Period (h)		Mid-Point Time (h)	Subject ID		
Mean	SD	CV%			
Pre-dose			NC	NC	NC
0-2	1		NC	NC	NC
2-4	3		NC	NC	NC
4-6	5		0.013	0.016	122.1
6-8	7		0.024	0.019	78.4
8-10	9		0.026	0.023	86.7
10-12	11		0.029	0.021	87.3
12-14	13		0.029	0.026	87.9
14-16	15		0.029	0.021	72.4
16-24	20		0.041	0.021	54.1
24-36	30		0.023	0.023	72.7
36-48	42		0.023	0.011	41.3
48-72	60		0.028	0.019	31.0
72-96	84		0.028	0.023	64.3
96-120	108		NC	NC	NC
120-144	132		NC	NC	NC
144-168	156		NC	NC	NC

Table 3. Cumulative % Dose Excreted into the Urine by Time Period, with Summary Statistics.

Time Period (h)		Mid-Point Time (h)	Subject ID		
Mean	SD	CV%			
Pre-dose			0	0	NC
0-2	1		0.026	0.028	147.13
2-4	3		0.050	0.026	123.27
4-6	5		0.070	0.022	108.35
6-8	7		0.094	0.021	91.66
8-10	9		0.099	0.023	91.66
10-12	11		0.109	0.160	94.48
12-14	13		0.128	0.128	92.46
14-16	15		0.167	0.146	87.64
16-24	20		0.228	0.191	83.97
24-36	30		0.272	0.213	78.29
36-48	42		0.296	0.221	74.33
48-72	60		0.317	0.227	71.41
72-96	84		0.322	0.228	70.36
96-120	108		0.328	0.229	69.87
120-144	132		0.329	0.228	69.44
144-168	156		0.322	0.222	69.21

Table 4. Urinary Excretion Rate (% Dose Excreted/h) by Time Period, with Summary Statistics.

Time Period (h)		Mid-Point Time (h)	Subject ID		
Mean	SD	CV%			
Pre-dose			0	0	NC
0-2	1		NC	NC	NC
2-4	3		0.002	0.002	121.00
4-6	5		0.002	0.002	102.00
6-8	7		0.001	0.002	79.12
8-10	9		0.002	0.002	92.14
10-12	11		0.002	0.002	108.01
12-14	13		0.001	0.002	97.43
14-16	15		0.004	0.002	71.39
16-24	20		0.002	0.004	84.99
24-36	30		0.002	0.002	72.19
36-48	42		0.001	0.002	41.39
48-72	60		0.002	0.002	51.04
72-96	84		0.002	0.002	73.16
96-120	108		NC	NC	NC
120-144	132		NC	NC	NC
144-168	156		NC	NC	NC

Table 5. % Dose Excreted into the Feces by Time Period, with Summary Statistics.

Time Period (h)		Mid-Point Time (h)	Subject ID		
Mean	SD	CV%			
Pre-dose			0	0	NC
0-12	6		0.0012	0.0013	114.0
12-24	18		0.2158	0.2083	96.4
24-48	36		0.1452	0.1796	104.7
48-72	60		0.0787	0.0830	106.0
72-96	84		0.0260	0.0250	93.0
96-120	108		0.0098	0.0100	101.7
120-144	132		0.0043	0.0036	84.3
144-168	156		0.0014	0.0011	73.4

Table 6. Cumulative % Dose Excreted into the Feces by Time Period, with Summary Statistics.

Time Period (h)		Mid-Point Time (h)	Subject ID		
Mean	SD	CV%			
Pre-dose			0	0	NC
0-12	6		0.001	0.001	153.49
12-24	18		0.145	0.196	135.21
24-48	36		0.310	0.272	119.96
48-72	60		0.289	0.447	114.96
72-96	84		0.411	0.471	114.39
96-120	108		0.431	0.473	112.31
120-144	132		0.435	0.472	111.06
144-168	156		0.426	0.472	110.21

Table 7. Fecal Excretion Rate (% Dose Excreted/h) by Time Period, with Summary Statistics.

Time Period (h)		Mid-Point Time (h)	Subject ID		
Mean	SD	CV%			
Pre-dose			0	0	NC
0-12	6		0.0001	0.0001	114.03
12-24	18		0.0100	0.0174	96.80
24-48	36		0.0089	0.0073	108.73
48-72	60		0.0023	0.0033	107.97
72-96	84		0.0011	0.0010	93.01
96-120	108		0.0004	0.0004	101.70
120-144	132		0.0002	0.0002	84.49
144-168	156		0.0001	0.0000	73.39

NC Not calculable
ns Not available

Table 11 Whole Blood Concentrations of Total Radioactivity by Time, with Summary Statistics.

Whole Blood Concentration (pg-cq/ml)						
Time (h)	Subject ID No.					
	Mean	SD	CV%	Minimum	Maximum	
Pro-dose	NC	NC	NC	0	0	
2	NC	NC	NC	0.00	0.00	
4	NC	NC	NC	0.00	16.89	
6	NC	NC	NC	0.00	63.71	
8	65.85	108.45	164.71	0.00	284.10	
10	NC	NC	NC	0.00	145.06	
12	NC	NC	NC	0.00	230.61	
14	NC	NC	NC	0.00	179.53	
16	NC	NC	NC	0.00	165.31	
18	NC	NC	NC	0.00	86.46	
20	NC	NC	NC	0.00	32.52	
24	NC	NC	NC	0.00	0.00	
30	NC	NC	NC	0.00	0.00	
36	NC	NC	NC	0.00	0.00	
48	NC	NC	NC	0.00	37.81	
60	na	na	na	na	na	
72	NC	NC	NC	0.00	0.00	
120	NC	NC	NC	0.00	0.00	
168	NC	NC	NC	0.00	0.00	

Table 12 Plasma Concentrations of Total Radioactivity by Time, with Summary Statistics.

Plasma Concentration (pg-cq/ml)						
Time (h)	Subject ID No.					
	Mean	SD	CV%	Minimum	Maximum	
Pro-dose	NC	NC	NC	0.00	0.00	
2	NC	NC	NC	0.00	12.4	
4	NC	NC	NC	0.00	62.8	
6	52.6	82.5	157	0.00	209	
8	82.1	129	157	0.00	338	
10	97.3	165	169	0.00	429	
12	95.6	156	164	5.52	406	
14	74.1	138	186	0.00	347	
16	67.5	121	179	0.00	307	
18	NC	NC	NC	0.00	251	
20	NC	NC	NC	0.00	201	
24	NC	NC	NC	0.00	165	
30	NC	NC	NC	0.00	110	
36	NC	NC	NC	0.00	65.8	
48	NC	NC	NC	0.00	34.9	
60	na	na	na	na	na	
72	NC	NC	NC	0.00	31.9	
120	NC	NC	NC	0.00	7.36	
168	NC	NC	NC	0.00	5.69	

NC Not calculable
na Not available

5) Study R168-152-8606:

PHARMACOKINETICS OF AGN 190168 0.1% GEL FOLLOWING SINGLE-DOSE AND MULTIPLE-DOSE TOPICAL ADMINISTRATION TO HEALTHY SUBJECTS
(Study date: Feb.-Mar., '93, Volume 1.72)

INVESTIGATOR AND LOCATION:

OBJECTIVES:

To evaluate the plasma concentration-time profiles following single and multiple-dose topical applications of a 0.1% AGN 190168 gel formulation to approximately 20% of the body surface area of 24 healthy male adult volunteers.

FORMULATION:

Formulation 8606X; Non-aqueous to aqueous phase addition used in the manufacture.

STUDY DESIGN:

The study included a single drug application followed by a 48-hour evaluation period (Study Day 1-3), and multiple drug applications (once daily for 7 days) followed by a 60-hour evaluation period after the last dose (Study Days 3-12). Approximately 6.8 g of gel (2 mg/cm²) was applied to 20% of the total body surface area (face, neck, chest, abdomen, frontal thigh). Each drug application was removed 12 hours post-dose by a brief shower. Twenty four male subjects entered and completed the study.

Sample Collections - Blood samples were collected according to the following schedule:

pre-dose, and at 2, 4, 6, 8, 10, 12, 13, 14, 15, 16, 18, 20, 24, 36 and 48 hours post-dose. prior to drug application on Study Days 5, 7 and 8.

prior to last dose, and 2, 4, 6, 8, 10, 12, 13, 14, 15, 16, 18, 20, 24, 36, 48 and 60 hours post last dose.

ASSAY:

DATA ANALYSIS:

Analysis of Variance procedures were performed on pharmacokinetic parameters (AUC₂₄, AUC_{TLDC}, AUC_{INF}, C_{MAX}, T_{MAX}, Ratio of parameters, K_{EL}, T_{1/2}) to compare the first and last doses. For calculations of AUC, values of 0.025 ng/mL were assigned to the below limit of quantitation values which occurred immediately after the last quantifiable concentration.

ANOVA procedures were also performed on log-transformed data to obtain geometric means and calculate a 90% confidence interval using a two one-sided t-test on these means.

RESULTS:

Plasma concentrations of the parent compound were below the quantitation limit of ng/mL following single and multiple dosing with a % gel. After the first dose, the C_{max} of the metabolite was 0.36 ± 0.19 ng/mL and AUC_{0-inf} was 15.8 ± 8.4 ng.h/mL. The plasma metabolite concentrations increased during chronic treatment to a mean C_{max} of $0.72 (\pm 0.58)$ ng/mL and a mean AUC of 19.2 ± 10.4 ng.h/mL. The highest C_p observed among all individuals was 2.89 ng/mL. The apparent t_{1/2} decreased over time to approximately 18 hours. Steady state was not reached after multiple dosing for 7 days. Time-dependent disposition was observed in plasma concentration-time profiles of the free acid metabolite and a negative slope (- 0.016) was obtained upon regression of the trough levels on Days 5, 7, 8 and 9. The sponsor explained that this might be a result of the retinoid's pharmacological effect (e.g. erythema, skin irritation or thinning of the stratum corneum). Alternatively, the dose might not have been applied and kept on the skin in a consistent manner throughout the study.

Adverse events were predominantly local effects in nature, including rash (87.5%), pruritis (83.3%) and desquamation (50.0%) at the application sites. Two cases of systemic adverse events (dizziness and headache) occurred and were considered not related to the subject medication. No subject was terminated because of the adverse events.

Comments:

1. After a single dose using the % gel, the t_{1/2} of the active metabolite was determined to be hrs in this study, which is quite different from t_{1/2} values determined from other studies. For example, the t_{1/2} was found to be hrs in Study R168-151-7997.
2. The T_{max} for the last dose of the multiple dosing portion of the study was hours which occurred earlier than the dose removal (at hours).
3. The AUC_{24h} for the last dose ng-h/ml) is about % of the AUC_{inf} for the first dose (in the single dose portion of the study). However, for the first dose, the AUC_{0-TLDC} was ng.h/ml and the AUC_{inf} was ng.h/ml. The difference between the two values was almost % of the AUC_{inf} which indicates the 48 hour sampling time for the first dose may be too short to accurately determine the AUC_{inf} and t_{1/2}.
4. The sponsor claimed a negative slope (- 0.016) upon regression of the trough levels on Days 5, 7, 8 and 9. This is biased since the levels on Day 10 (at 24 hours after the Day 9 dose) should also be included in the regression.

Allergan, Inc.

Table 9.1.1

A Summary of the Pharmacokinetic Parameters for AGN 190299 After Topical Dosing* with a 0.1% AGN 190168 Gel

(n=24, except where indicated)

Pharmacokinetic Parameters	First Dose	Last Dose	p-value
AUC ₀₋₂₄ (ng·h/ml) [range]	4.55 ± 2.05	10.1 ± 7.2	0.0003
AUC _{0-TLDC} (ng·h/ml) [range]	8.15 ± 3.54	14.5 ± 9.8	0.0004
AUC _{0-INF} (ng·h/ml) [range]	15.8 ± 8.4†	19.2 ± 10.4†	0.1552
C _{MAX} (ng/ml) [range]	0.36 ± 0.19	0.72 ± 0.58	0.0058
T _{MAX} (h) [range]	13.5 ± 3.5	8.75 ± 3.57	0.0001
K _{EL} (1/h) [range]	0.0243 ± 0.0114†	0.0394 ± 0.0152†	0.0012
t _{1/2} (h) (harmonic mean) [range]	28.5 ± 13.6†	17.6 ± 6.7†	0.0033

* Approximate dosage of 0.1% AGN 190168 gel was 0.1 mg/kg/day over 20% body surface area.

† n=22, P-value from cross-over analysis of variance.

R168-152-8606

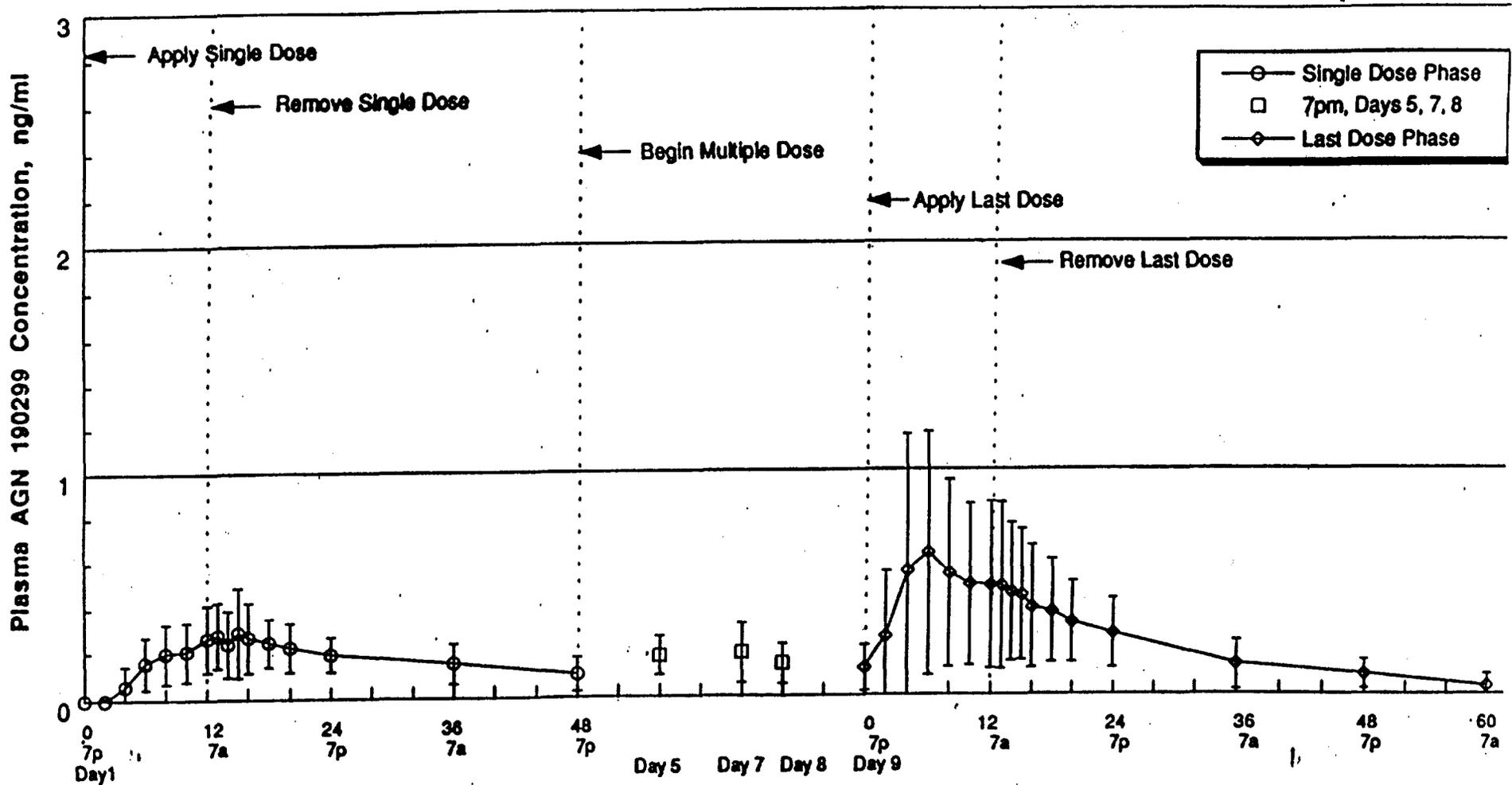


Figure 9.2.1. Plasma AGN 190299 concentration in human volunteers after single and multiple topical dosing of a 0.1% AGN 190168 gel over 20% body surface area. Data are expressed as mean \pm SD (n = 24).

SUBJECT CHARACTERISTICS
Study No. R168-152-8606

SUBJECT NUMBER	SUBJECT INITIALS	RACE	AGE (Years)	HEIGHT (Inches)	WEIGHT (Pounds)	FRAME	WEIGHT RANGE (Pounds)
		Asian	23	69	171	Medium	
		Cauc	20	71	189	Large	
		Cauc	21	71	170	Medium	
		Cauc	20	72	189	Large	
		Cauc	27	73	183	Medium	
		Cauc	21	72	182	Medium	
		Cauc	24	73	175	Medium	
		Cauc	21	75	230	Large	
		Cauc	22	69	194	Large	
		Cauc	21	67	150	Small	
		Cauc	21	70	198	Large	
		Cauc	22	67	158	Medium	
		Cauc	20	73	169	Medium	
		Cauc	20	72	181	Medium	
		Cauc	22	73	166	Medium	
		Cauc	22	72	184	Medium	
		Cauc	20	69	175	Medium	
		Cauc	27	77	207	Large	
		Cauc	25	68	161	Medium	
		Cauc	21	78	209	Large	
		Cauc	22	68	143	Medium	
		Black	24	70	185	Large	
		Cauc	21	73	210	Large	
		Cauc	23	74	200	Large	
	Means		22.1	71.5	182.5		

Allogon, Inc. Study R168-152-8606, Metabolite AGN 190299 of AGN 190148 (Acetylenic retinoid) 3
Summary of parameters for the FIRST-DOSE phase 18:25 Thursday, February 9, 1995

SUBJECT	AUC 0-24 (ng-h/mL)	AUC _{0-∞} (ng-h/mL)	AUC ₀₋₁₂ (ng-h/mL)	C _{max} (ng/mL)	T _{max} (h)	K _{el} (1/h)	t 1/2 (h)
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MEAN	4.35	8.15	13.82	0.34	13.30	0.0243	26.5
STD	2.05	3.34	6.39	0.19	3.51	0.0114	19.3
C.V.	44.94	43.39	53.66	52.89	26.05	44.9290	53.4
MIN	0.70	0.70	4.14	0.09	6.00	0.0079	14.0
MAX	8.49	14.13	39.89	0.82	20.00	0.0496	67.0
N	24.00	24.00	22.00	24.00	24.00	22.0000	22.0

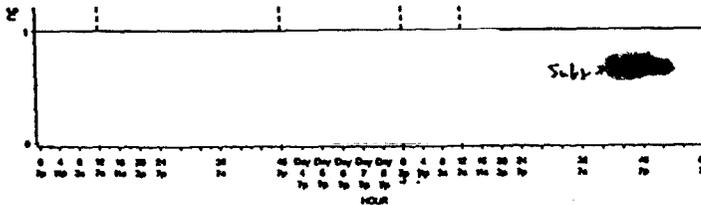
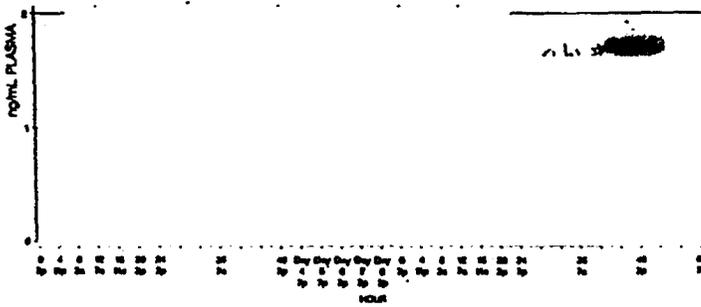
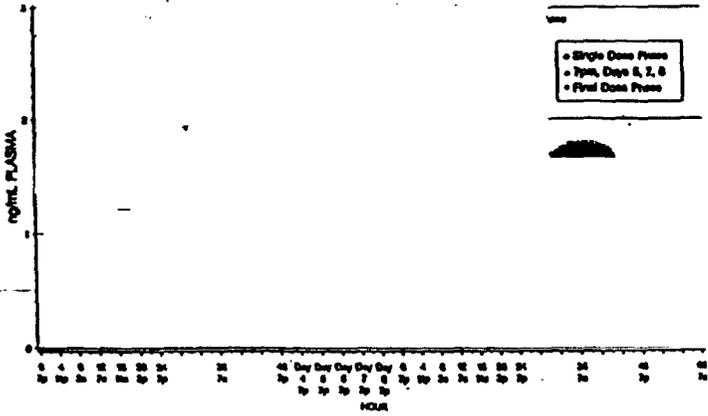
Allogon, Inc. Study R168-152-8606, Metabolite AGN 190299 of AGN 190148 (Acetylenic retinoid) 4
Summary of parameters for the LAST-DOSE phase 18:25 Thursday, February 9, 1995

SUBJECT	AUC 0-24 (ng-h/mL)	AUC _{0-∞} (ng-h/mL)	AUC ₀₋₁₂ (ng-h/mL)	C _{max} (ng/mL)	T _{max} (h)	K _{el} (1/h)	t 1/2 (h)	AUC 0-24 Ratio LAST/FIRST	AUC _{0-∞} Ratio LAST/FIRST	AUC 0-24 last/ AUC first
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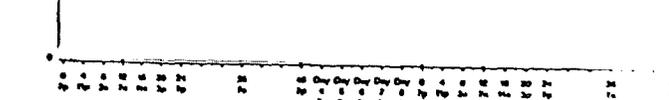
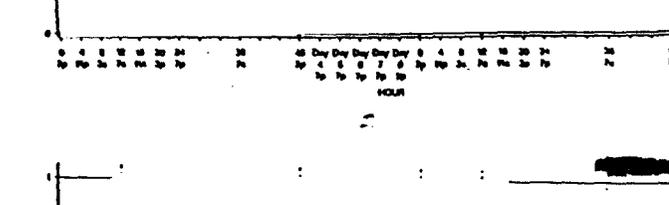
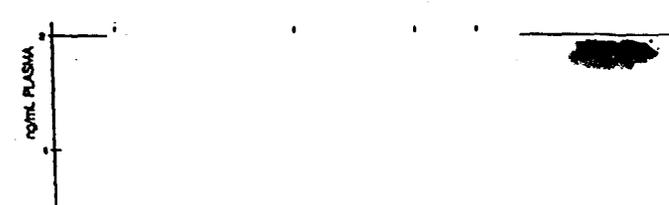
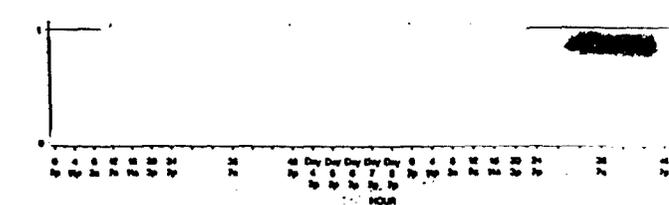
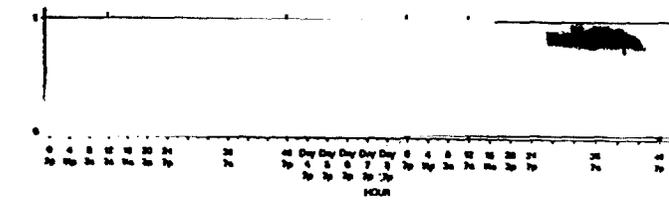
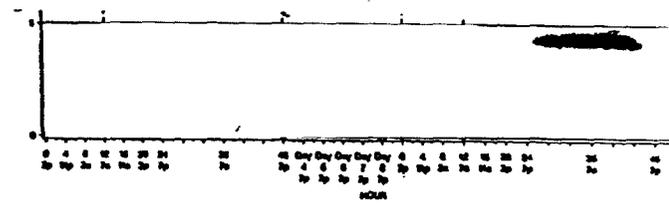
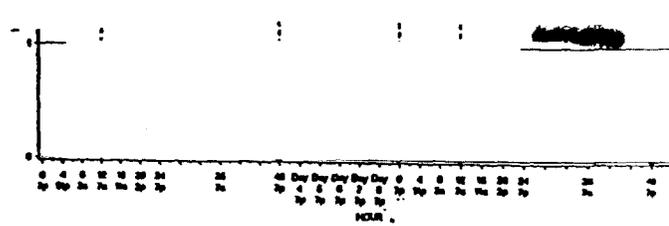
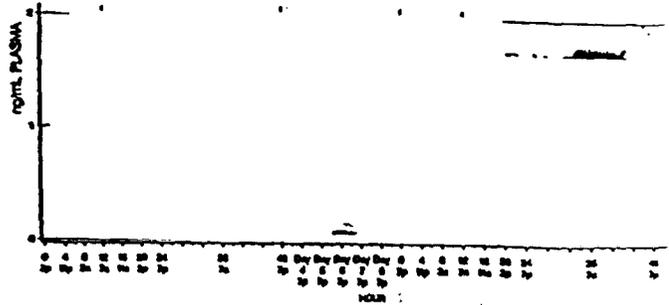
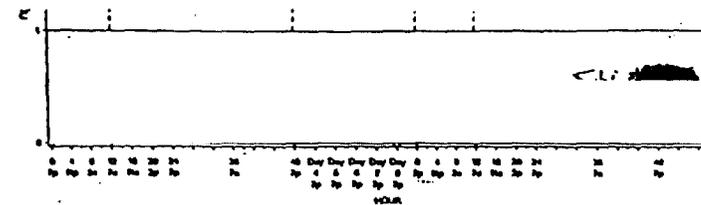
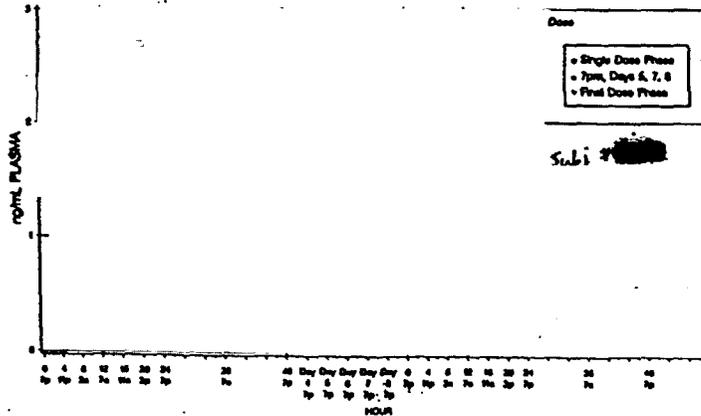
MEAN	10.05	14.50	19.15	0.72	6.75	0.0394	17.6	2.49	1.45	0.76
STD	7.23	9.76	10.43	0.58	3.57	0.0132	18.0	1.47	0.60	0.44
C.V.	71.98	67.32	54.45	80.77	52.88	33.527	81.7	59.82	41.37	58.44

Plasma AGN 190299 Concentration versus Time

Allergan Study R168-152-8606, Subject [REDACTED]

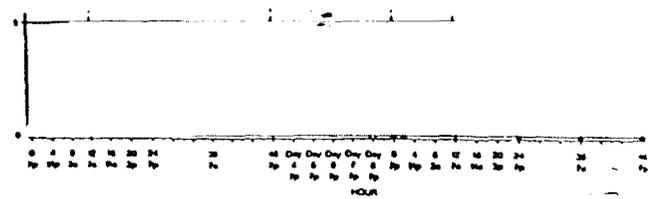
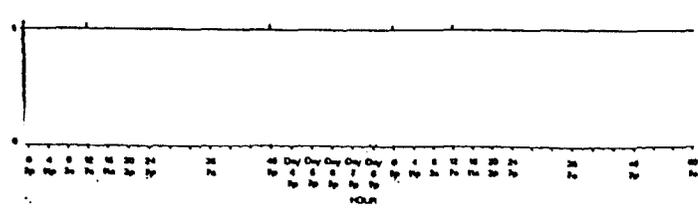
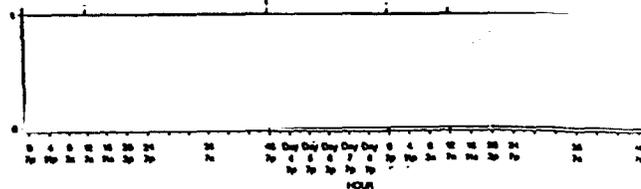
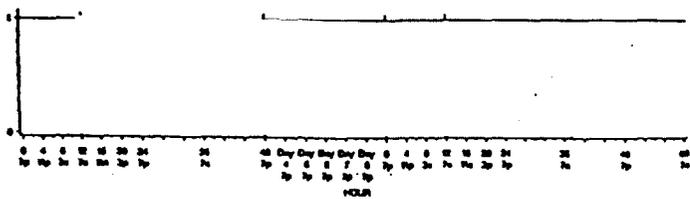
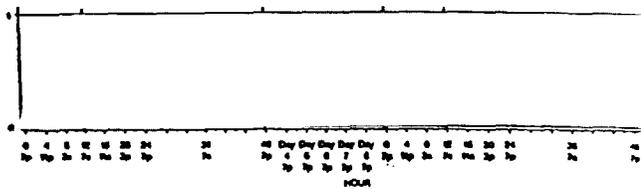
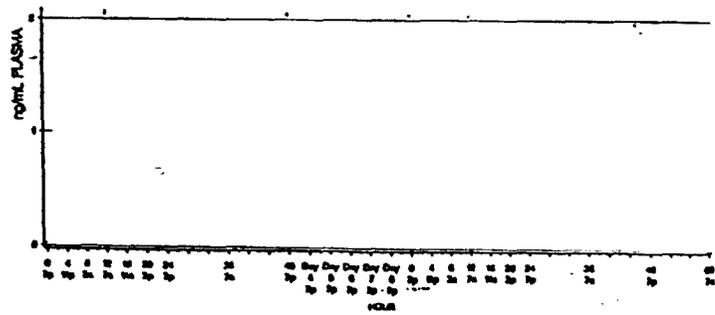
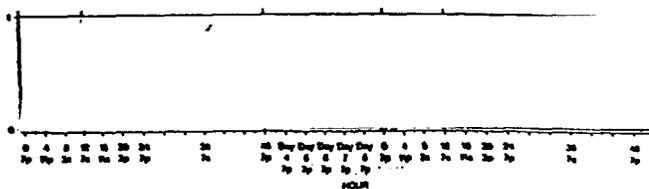
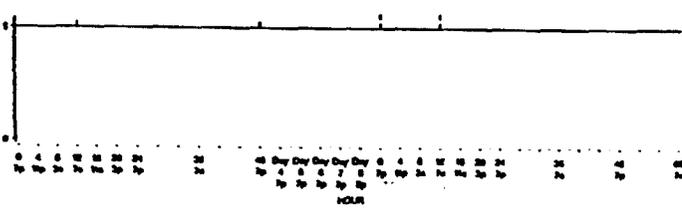
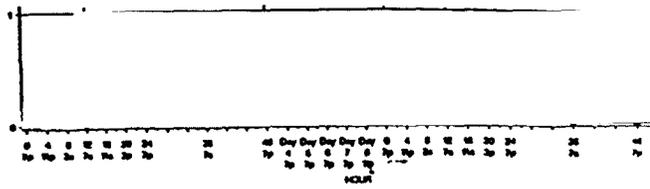
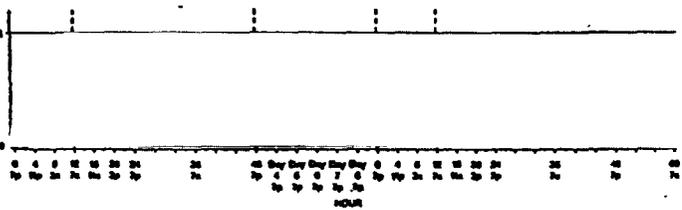
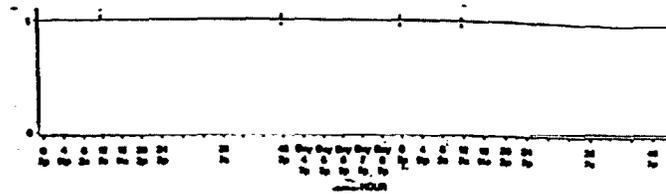
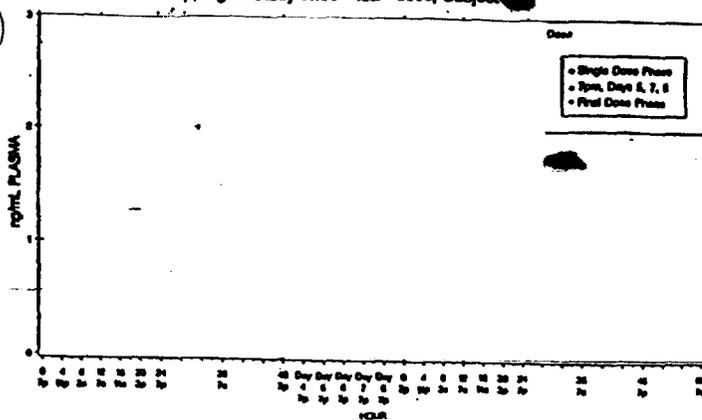


Allergan Study R168-152-8606, Subject 104



Plasma AGN 190299 Concentration versus Time

Allergan Study R168-152-8606, Subject [REDACTED]



PERCUTANEOUS ABSORPTION AND MASS BALANCE OF ¹⁴C-AGN 190168 0.1% GEL FOLLOWING TOPICAL ADMINISTRATION TO HEALTHY SUBJECTS

INVESTIGATOR AND LOCATION:

OBJECTIVES:

To evaluate the percutaneous absorption and mass balance of ¹⁴C-tazarotene 0.1% gel following a single topical application to healthy subjects.

FORMULATION: 7997X-¹⁴C

STUDY DESIGN:

This was a single-center, open-label study. Six healthy male subjects (age: 22.6±2.4 yrs., wt: 178.7±32.1 lb, ht: 70.4±3.0 in) entered and completed the study. Subjects were confined for the first 24 hours and each received a single application of ¹⁴C-tazarotene 0.1% gel (170 µCi/2 g gel) to the back and sides of the trunk (800 cm²). After one hour, the treated area was occluded with plastic wrap. After a further nine hours, the plastic wrap was removed and the treated area was washed with four isopropanol-soaked gauze pads to remove the unabsorbed drug. No showers were allowed until 24 hours after the application.

Sample collections -

Tape strippings and skin biopsies: on Day 0 at 10 hours after application (after drug removal), an area (5.1cm x 20 cm) was taped stripped to glistening (about 20 strips) and two 3mm biopsies were taken within this area. On Day 7, tape stripping was performed again on a separate area.

Skin sloughings: After biopsies on Day 0, subjects wore tight T-shirt to trap radioactive material subsequently shed from the skin surface. At 24 hours, the T-shirt was removed and the application site washed with four isopropanol-soaked gauze pads. A new T-shirt was worn from 24-48 hours and the application site washed again.

Blood samples: At 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48 and 72 hours post-dose; stored frozen until analysis.

Urine samples: 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-16, 16-24 hrs, and 12 hr intervals thereafter for a total of 6 days; Stored frozen until analysis.

Stool specimens: Collected for 6 days.

ASSAY:

RESULTS:

The average dose was found to be 1.94 ± 0.02 g, equivalent to a dosing density of 2.43 mg gel per cm^2 . No radioactivity was found in the 2 hr urine specimen of any subject and very low amounts in the 4-hr specimen. The urinary excretion rate increased rapidly from 4-12 hours and then gradually declined with a $t_{1/2}$ of 17-18 hours. Most of the radioactivity was excreted within 48 hours. The total urinary excretion was _____ % of the applied dose.

The stool data showed a maximum excretion at Days 2-3 and was equal to approximately 1%. The mean fecal excretion for all subjects was 2.69 ± 1.23 % of the applied dose. Subjects showing the highest urinary excretion also had the highest fecal excretion of radioactivity. The total urinary and fecal excretion amounted to about 5.3%.

Like the urine data, no radioactivity was found in the 2 hour plasma and only very low levels in the 4-hour plasma. Subsequently, the levels increased to a peak at 10-12 hours followed by a decline thereafter. The mean peak concentration in plasma as based on radioactivity was $2.06 (\pm 0.90)$ ng-eq/mL. The levels in the packed red blood cells paralleled the plasma content but only achieved about one-fifth the measured plasma concentration.

Data obtained from tape strippings at 10 hours after application indicated a mean of 0.76 ± 0.08 % of the dose was found in the stratum corneum of the 102 cm^2 strip site following the skin wash, which is equivalent to 5.96 ± 0.62 % of the dose when extrapolated to the total 800 cm^2 area of application. The distribution of radioactivity across the depth of stratum corneum appeared to decrease exponentially. Recovery from the skin biopsies indicated that a mean of 2.03 ± 1.41 % of the dose was in the epidermis and dermis.

The unabsorbed drug from the skin surface as recovered from spatula, gauze pads and PE film was _____ %. An additional _____ % was recovered from T-shirt and gauze pads used during the 24 and 48 hour skin washes. When these amounts were added to that found in the excreta, approximately 80% of the applied dose can be accounted for.

None of the subjects demonstrated any systemic side effects or experienced any adverse reactions at the site of drug application.

TABLE 1
Volunteer Demographics

Subject ID	Sex	Race	Age	Height (In)	Weight (lb.)
	M	W	22	67.5	140
	M	W	23	66	157
	M	W	20	72	160
	M	W	23	71	224
	M	W	27	74	206
	M	W	21	72	185
Mean			22.6	70.4	178.7
Std. Dev.			± 2.4	± 3.0	± 32.1

Table 2

Mass Balance Summary
% Applied Dose

Source	Average	SE
10 hr Wash: *	66.444	2.294
24-48 hr Wash: **	7.474	0.728
Urine Recovery:	2.612	0.333
Stool Recovery:	2.689	0.501
Tape Strip:	0.764	0.077
Total Recovery:	79.983	2.629

*: Includes Saran cover, spatula and gauze.
 **: Includes T-shirt and gauze.

TABLE 3

Biopsy Radioactivity

Subject	DPM-Bkg	DPM/biopsy	% Dose ETA*
Mean ± SD			3.2 ± 1.41

* Extrapolated to Total area of Application.

APPEAR THIS WAY
ON ORIGINAL

Table 4
Urine Excretion Summary
% Applied Dose/hr

Sample #	Average	SE	Mid-T (hr)
1	0.000	0.00	
2	0.004	0.00	
3	0.046	0.01	
4	0.132	0.03	
5	0.187	0.03	
6	0.214	0.02	
7	0.147	0.03	
8	0.114	0.02	
9	0.058	0.01	
10	0.018	0.00	
11	0.007	0.00	
12	0.005	0.00	
13	0.003	0.00	
14	0.002	0.00	
15	0.001	0.00	
16	0.001	0.00	
17	0.000	0.00	

Table 5
Stool Recovery Summary
% Applied Dose

Sample # (Day)	Average
1	0.125
2	0.40
3	0.79
4	0.50
5	0.13
6	0.07
7	0.17
8	0.12
Totals:	2.689 ± 1.228

*: Missing values are days when no sample was provided by volunteer.

APPEAL THIS WAY
ON ORIGINAL

Table 6
Tape Strip Summary
% Applied Dose

Sample #	Average	SE
1	0.180	0.022
2	0.078	0.010
3	0.072	0.014
4	0.054	0.006
5	0.057	0.007
6	0.052	0.009
7	0.048	0.010
8	0.028	0.004
9	0.027	0.006
10	0.021	0.006
11	0.022	0.004
12	0.018	0.005
13	0.022	0.005
14	0.019	0.005
15	0.012	0.002
16	0.015	0.003
17	0.010	0.002
18	0.010	0.002
19	0.010	0.002
20	0.010	0.002
Total	0.764	0.007

Table 7

**Plasma Concentration Summary
Nanogram-equivalents drug/ml**

Sample #	Average	SE	Time (hr)
1	0.000	0.000	
2	0.101	0.029	
3	0.814	0.230	
4	1.560	0.352	
5	2.011	0.360	
6	2.040	0.371	
7	1.505	0.250	
8	1.179	0.174	
9	0.720	0.136	
10	0.353	0.080	
11	0.305	0.075	
12	0.109	0.040	

*: Data not available.

Table 8

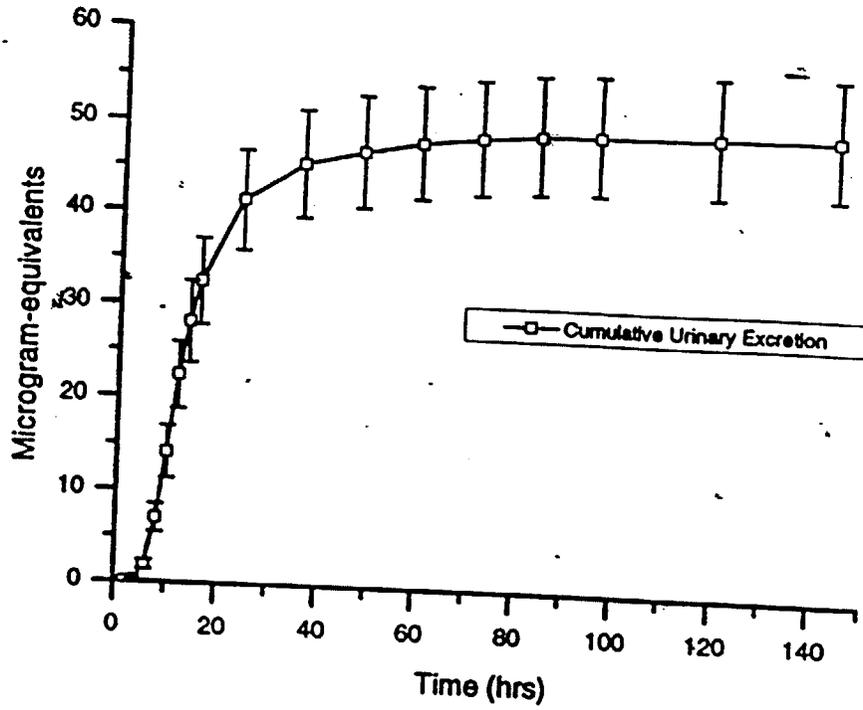
**Packed Red Blood Cell Concentration Summary
Nanogram-equivalents drug/ml**

Sample #	Average	SE	Time (hr)
1	0	0	
2	0.002	0.002	
3	0.095	0.043	
4	0.223	0.062	
5	0.371	0.084	
6	0.404	0.101	
7	0.276	0.063	
8	0.189	0.041	
9	0.064	0.024	
10	0.029	0.017	
11	0.016	0.01	
12	0.01	0.007	

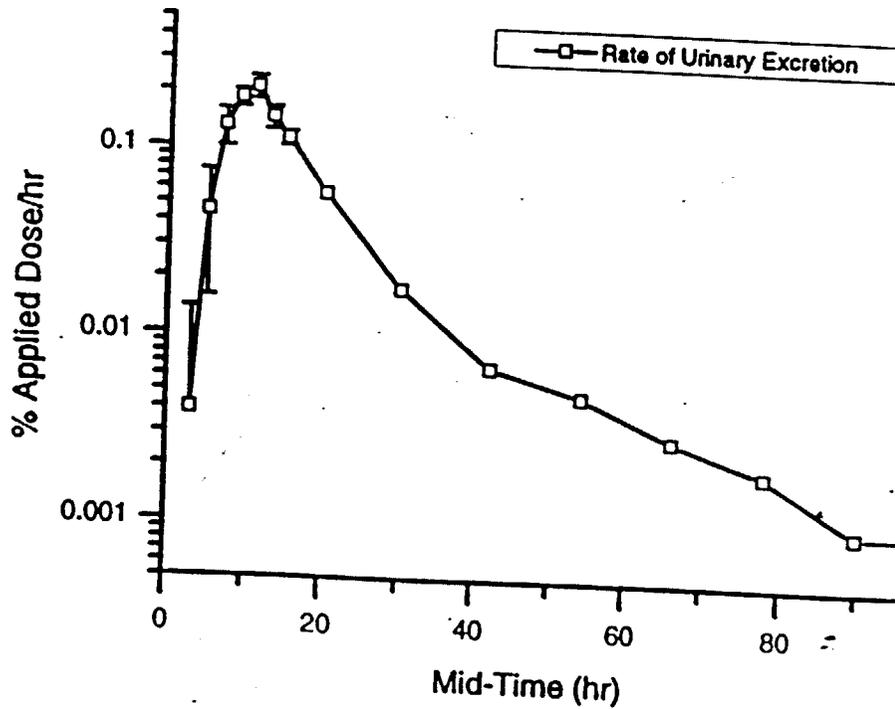
*: Data not available.

Figure 1

(a)



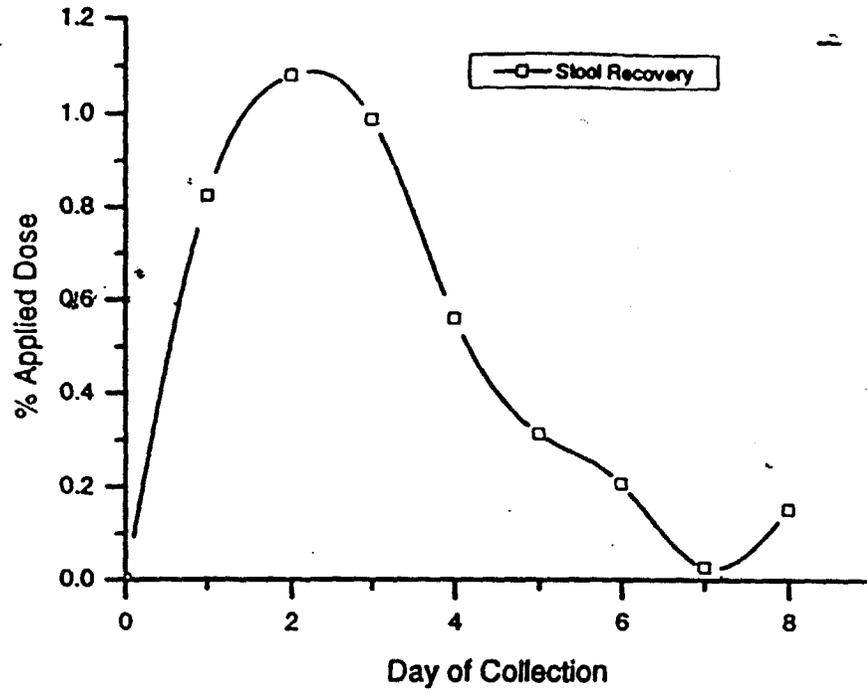
(b)



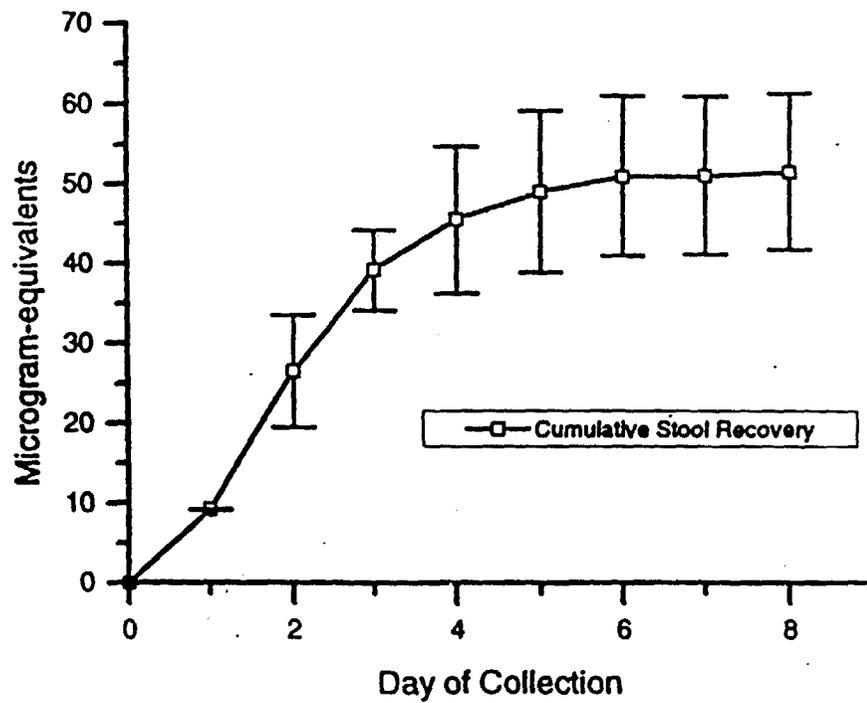
Rate of Urinary Excretion (mean \pm SE) plotted from the data in Table 3.

Figure 2

(a)



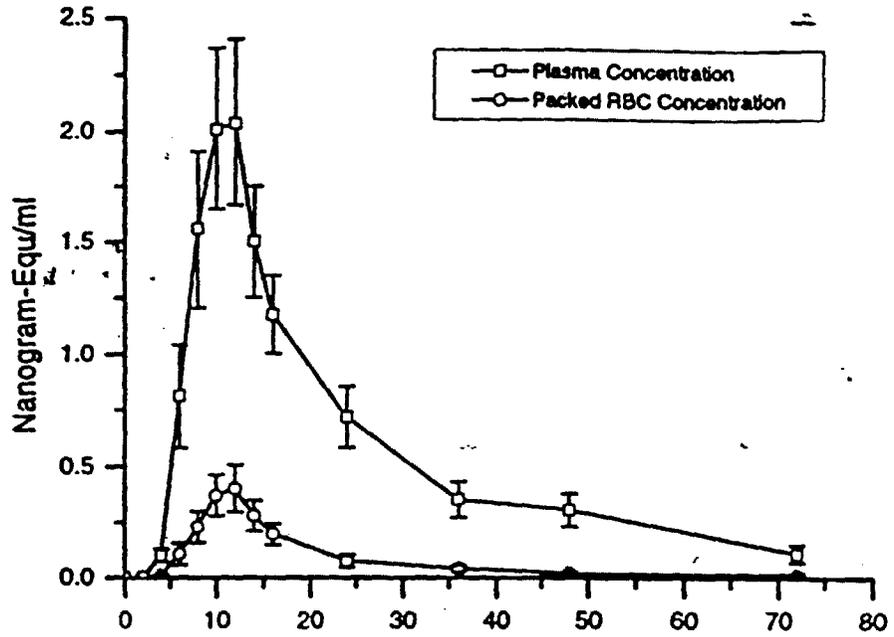
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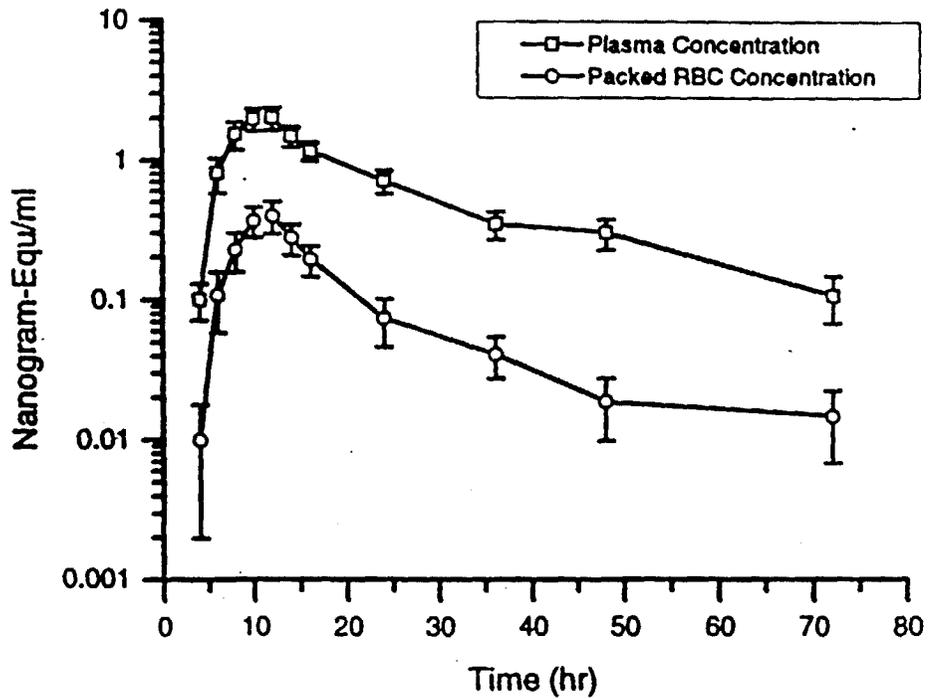
Upper Panel: Stool recovery (mean) plotted from the data in Table 6.
Lower Panel: Cumulative (mean ± SE) stool recovery.

Figure 3

(a)

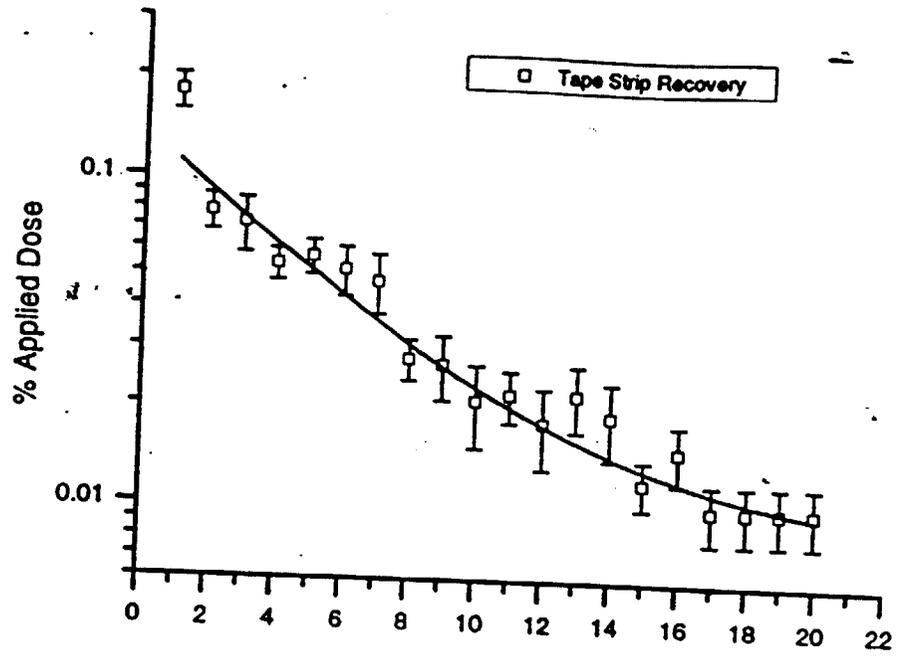


(b)



Plasma and packed RBC concentrations (mean \pm SE) plotted from the data in Tables 4 and 5. Upper Panel in linear scale format; Lower Panel in semi-log scale format.

Figure 4



Tape strip recovery (mean \pm SE) across 20 individual strips plotted from the data in Table 7. Line represents a fitting of the data.

PHARMACOKINETICS OF AGN190168 ADMINISTERED AS A SINGLE INTRAVENOUS INFUSION DOSE AND AS A SINGLE TOPICAL DOSE (0.1% GEL) TO HEALTHY SUBJECTS

INVESTIGATOR AND LOCATION:

Primary Investigator:

OBJECTIVES:

1. To determine the pharmacokinetic profile of tazarotene and the active metabolite following a single intravenous infusion dose of tazarotene to healthy subjects.
2. To determine the rate and extent of absorption of tazarotene and the active metabolite after a single topical dose of tazarotene 0.1% gel by comparison with the intravenous infusion data.
3. To assess the safety of tazarotene after topical and intravenous administration.

FORMULATION:

IV solution: 0.01% w/v in 45% w/w ethanol.

Gel: Formulation 8606X

STUDY DESIGN:

This is a 2 period, cross-over study. Eight male subjects (age: 31.1 ± 8.5 yrs, wt: 73.1 ± 7.6 kg) entered the study, each received an IV infusion dose and a topical dose with a washout period of 13 to 15 days. Subjects remained confined 72 hr following each dose.

Drug administration -

- i) IV-infusion dose: The dose was administered over a 20 minute period in the morning. The total amount of tazarotene administered was approximately $15 \mu\text{g}/\text{kg}$ in a volume of approximately 10-15 mL. (Because of the known adsorption of the drug onto the syringe, filter and tubing, a 19% overage by volume was administered).
- ii) Topical dose: The 0.1% gel was applied to 20% of the total body surface area at $2 \text{ mg}/\text{cm}^2$ (equivalent to $107 \mu\text{g}/\text{kg}$) in the evening, and the actual dose for each subject was recorded. The application area remained uncovered for 2 hr while the gel dried and afterwards it was covered with standard light, non-occlusive nighttime clothing. The dose was removed during showering 12 hr later.

Sample collections -

i) IV infusion phase:

Blood samples: pre-dose, 5, 10, 15, 20 following start of infusion, 2, 5, 10, 15, 30, 45, 60, 90 minutes, and 2, 3, 4, 6, 9, 12, 17, 24, 30, 36, 42, 48, 60 and 72 (27 samples)

hr following the end of infusion.
Urine and feces: pre-dose, 0-12, 12-24, 24-48, 48-72 hrs.

ii) Topical phase:

Blood samples: pre-dose, 3, 6, 9, 12, 14, 17, 20, 24, 30, 36, 42, 48, 60 and 72 hr post-dose.

Urine samples: pre-dose, 0-12, 12-24, 24-48, 48-72 hrs post-dose

Fecal samples: Not collected.

All sample processing was performed under yellow light. Additional blood and urine samples were collected for laboratory testing at approximately two weeks prior to dosing, at 24 hr after infusion, and at 12 hr after topical dosing.

ASSAY:

Plasma samples:

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.

Terminal elimination rate constant (k):

a) For tazarotene:

In the infusion phase, the k value for each subject was calculated by regression of the linear portion of the semi-logarithmic concentration versus time plot of the last three quantifiable time points before the first BLQ value (but 6 to 12 hr and 12 to 24 hr for subjects [redacted] and [redacted], respectively). K values were not calculable for the topical phase.

b) For the active metabolite:

The k value for each subject was calculated by regression of the linear portion of the semi-logarithmic concentration versus time plot from 30 to 72 hr (or 30 to 60 hr for subjects [redacted] and 108) in the infusion phase, and 36 to 72 hr for the topical phase (the 48 hr time point was omitted for subject [redacted]).

$T_{1/2}$: Mean values are reported as harmonic means and the corresponding standard deviations

were calculated using a jackknife technique.

AUC: AUC_{0-24} , AUC_{0-48} and AUC_{0-inf} were calculated for each subject by the trapezoidal rule. The AUC associated with the terminal phase (AUC_k) was calculated for the IV infusion by dividing the extrapolated concentration of the terminal phase (at the midpoint of the infusion for tazarotene or the end of infusion for the active metabolite) by the terminal elimination rate constant, i.e.,

$$\begin{aligned} \text{For tazarotene: } AUC_k &= C_{0.1667}/k && \text{(midpoint of infusion: at 0.1667 hr)} \\ \text{For the active metabolite: } AUC_k &= C_{0.333}/k && \text{(end of infusion: at 0.333 hr)} \end{aligned}$$

MRT/MAT: The intrinsic mean residence time (MRT_{INTR}) for tazarotene and the active metabolite, and the mean absorption time of tazarotene after a topical dose ($MAT_{TAZ, TOP}$) were calculated as follows:

$$\begin{aligned} MRT_{TAZ, INTR} &= MRT_{TAZ, INF} - MIT_{TAZ, INF} \\ MRT_{MET, INTR} &= MRT_{MET, INF} - MRT_{TAZ, INF} \\ MAT_{TAZ, TOP} &= MRT_{MET, TOP} - MRT_{MET, INTR} \end{aligned}$$

MRT: Mean residence time MIT: Mean input time
TAZ: Tazarotene; MET: Active metabolite
INF: Infusion; TOP: Topical

The following PK parameters were also calculated:

<u>Tazarotene</u>	<u>Metabolite</u>
$CL_{TAZ} = \text{Dose}/AUC_{0-INF, TAZ}$	$(CL/F)_{MET} = \text{Dose}/AUC_{0-INF, MET}$
$V_{d, TAZ} = CL_{TAZ}/k_{TAZ}$	$V_{d, MET} / F_{MET} = (CL/F)_{MET} / k_{MET}$
$V_{ss, TAZ} = CL_{TAZ} \times MRT_{TAZ}$	$V_{ss, MET} = (CL/F)_{MET} \times MRT_{MET}$

Statistical analysis: Analysis of variance was performed using the following model.

$$Y = \mu + \text{treatment} + \text{sequence} + \text{subject}(\text{sequence}) + \text{period} + \text{error}$$

RESULTS:

A) IV infusion phase:

a) Plasma samples:

i) Tazarotene: After the IV infusion dose, the plasma tazarotene concentration rose rapidly to achieve a C_{max} of 17.8 ± 8.2 ng/mL at the end of the infusion period. The plasma concentration then declined very rapidly reaching approximately ng/mL by hr after the end of the infusion. The decline was biphasic with a terminal $t_{1/2}$ of hrs. Only % of the total AUC_{0-inf} was associated with the terminal phase, indicating that the majority of the dosed tazarotene was eliminated during the rapid decline phase. The clearance was L/hr/Kg, the volume of distribution was L/Kg, while the steady state volume of distribution (V_{ss}) was L/kg. The intrinsic mean residence time was

determined to be 1.56 ± 1.09 hr.

ii) Active metabolite (AGN190299):

The concentration of the active metabolite rose rapidly to reach concentrations higher than that of tazarotene with a mean C_{max} of 34.0 ± 5.05 ng/mL and mean T_{max} of 0.48 ± 0.26 hr after the end of the infusion. The plasma concentration then declined biexponentially with a terminal $t_{1/2}$ of 13.8 ± 2.2 hrs. The mean AUC_{0-inf} was 158 ± 25 ng.hr/mL and intrinsic mean residence time was 6.20 ± 2.44 hr.

b) Urine samples:

No tazarotene or AGN 190832 was detected in urine samples, and only one urine sample had detectable active metabolite. AGN 190844 was the major urinary metabolite and a total of $11.9 \pm 5.23\%$ of the IV dose was excreted into the urine as AGN 190844 within 72 hrs with the majority excreted within 12 hrs.

B) Topical dosing phase:

a) Plasma samples:

i) Tazarotene:

Tazarotene was detectable in many plasma samples owing to the improved assay method (ng/mL). After a single topical administration of 0.1% tazarotene gel, the mean C_{max} was 0.016 ± 0.006 ng/mL and the mean T_{max} was 12.0 ± 4.2 hrs.

ii) Active metabolite, AGN 190299:

Plasma concentrations of the active metabolite rose steadily to reach a C_{max} of _____ ng/mL at _____ hr post-dose. The decline from the C_{max} was monophasic with a half-life of _____ hr, which is comparable to the terminal half-life after IV infusion of tazarotene solution. By comparison of the AUC_{0-inf} values obtained from the infusion and topical doses, the bioavailability of the topical dose was found to be _____ % of the applied dose. The MRT of the metabolite after topical dose was _____ hr, yielding a MAT of _____ hr for topical dosing of tazarotene.

b) Urine samples:

Tazarotene, the active metabolite and metabolite AGN 190832 were not detected (_____ ng/mL) and only AGN 190844 was observed in urine samples. A total of _____ % of the topical dose was excreted into the urine collected up to 72 hrs post-dose and most occurred during the 12-24 hr and 24-48 hr collection period.

C) Intersubject variability:

There was low intersubject variability in the PK parameters of tazarotene and the active metabolite following an IV infusion of tazarotene. The greater variability observed in the PK parameters after a topical dose reflects the intersubject variation in both rate and extent of percutaneous absorption.

D) Adverse events:

The IV infusion dose was associated with signs and symptoms of irritation and inflammation (erythma, edema, pain, stinging, numbness) in and around the area of injection and some of these adverse events persisted for a prolonged period. The only adverse event following topical dosing was a single episode of treatment-unrelated syncope.

Comments:

1. The sponsor stated that 19% overage for the infusion dose was used due to adsorption of drug by infusion components but the supporting data are not provided.
2. The assay method and method validation results for the method used in this study are not provided.
3. Regarding the systemic exposure after a topical dose:
 - a. Assuming no adsorption loss for the infusion dose, the actual dose will be 1.2 times of the dose used in the calculation, and the absolute bioavailability for the topical dose will be 1.2 times of what the sponsor calculated.
 - b. The observed mean C_{max} and AUC_{0-inf} for the active metabolite after the topical dose in this study (C_{max} : 0.24 ± 0.17 ng/mL; AUC_{0-inf} : 6.25 ng.hr/mL) were comparable to the values observed in a previous single-dose study with 24 healthy subjects (C_{max} : 0.47 ± 0.25 ng/mL; AUC_{0-inf} : 14.6 ± 6.8 ng.h/mL).
 - c. The extent of systemic absorption after a single topical dose was determined to be .% from this study which is comparable to values obtained from previous studies.
4. Regarding the urine data:
 - a. Urine sample concentrations were provided without the urine sample volume data.
 - b. Excretion of the active metabolite within 72 hour post-dose for the topical dose was about 2.9% of that observed after the infusion dose, or 0.4% after correction for dose differences between the two administration routes.
 - c. Because of the low creatinine clearance observed (possibly due to incomplete collection of urine samples), and the fact that several samples were left at RT for an unspecified time period, the urine data was less emphasized in this study.
5. The elimination half-life of the active metabolite determined from the IV infusion dose was 13.8 ± 2.2 hrs. This indicates that the terminal phase of the active metabolite after a topical dose reflects the elimination rate rather than the absorption rate.

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Key Pharmacokinetic Results

Mean, S.D. and CV% data (n=8) of key results are presented as follows:

Parameter (Unit)	AGN 190168			AGN 190299		
	Mean	S.D.	CV%	Mean	S.D.	CV%
Intravenous Dosing						
AUC ₀₋₂₄ (ng•hr/mL)	8.47	1.50	17.7	146	24	16.5
AUC _{0-TLDC} (ng•hr/mL)	7.28	2.17	29.8	156	25	16.1
AUC _{0-INF} (ng•hr/mL)	7.40	2.22	29.9	158	25	15.8
%AUC in terminal phase	17.5	30.5	174.4	20.8	5.5	26.3
k (hr ⁻¹)	0.111	0.059	53.1	0.0503	0.0081	16.2
t _{1/2} (hr) (harmonic)	6.22	3.33	53.6	13.8	2.2	15.9
Cl* (L/hr/kg)	2.23	0.85	38.2	0.0970	0.0144	14.8
V _d * (L/kg)	26.1	15.6	59.6	1.97	0.38	19.5
V _{ss} * (L/kg)	3.55	2.08	58.8	0.750	0.244	32.5
AUMC _{0-INF} (ng•hr ² /mL)	13.5	9.4	69.6	1224	410	33.5
MRT (hr), <i>intrinsic</i>	1.56	1.09	69.6	6.20	2.44	39.4
Topical Dosing						
C _{max} (ng/mL)	0.0160	0.0055	34.3	0.241	0.173	71.6
t _{max} (hr)	12.0	4.2	35.4	18.6	6.1	32.5
AUC ₀₋₂₄ (ng•hr/mL)	NC	NC	NC	2.78	1.85	66.6
AUC _{0-TLDC} (ng•hr/mL)	NC	NC	NC	5.78	2.85	49.2
AUC _{0-INF} (ng•hr/mL)	NC	NC	NC	6.25	2.87	46.0
k (hr ⁻¹)	NC	NC	NC	0.0410	0.0072	17.5
t _{1/2} (hr)	NC	NC	NC	16.9	3.0	17.4
F (% Dose)	NC	NC	NC	0.550	0.219	39.8
AUMC _{0-INF} (ng•hr ² /mL)	NC	NC	NC	207	81	39.2
MRT (hr), <i>topical</i>	NC	NC	NC	35.0	7.0	20.0
MAT ₁₆₈ ^{skin} (hr)	28.8	8.5	29.7	NA	NA	NA

NC = Not calculable

NA = Not applicable

* Assuming F_m = 1 for AGN 190299

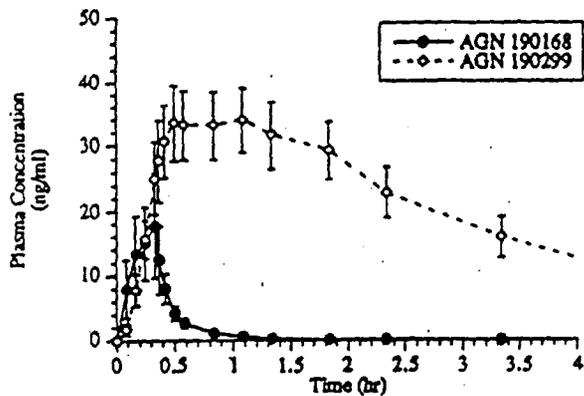
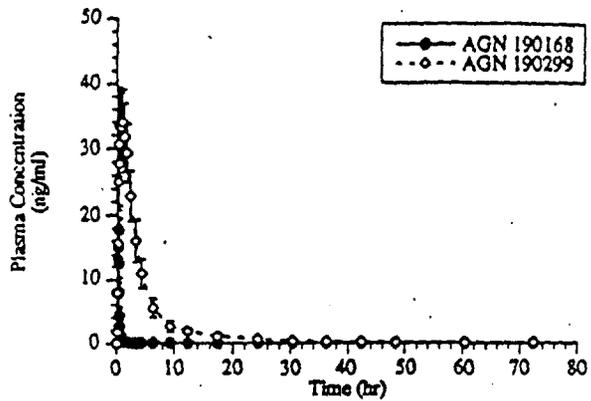


Figure 9.2.1

Plasma Concentration Versus Time Profiles of AGN 190168 and AGN 190299 Following a Single Intravenous Infusion Administration of AGN 190168 0.01% w/v Solution to Eight Healthy Subjects: Linear Plot (Mean \pm S.D.) Lower figure is expansion of upper figure.

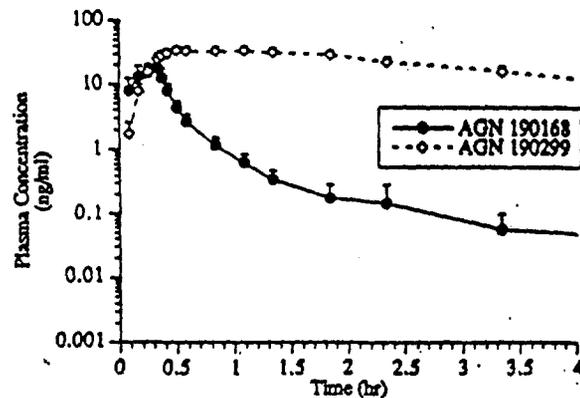
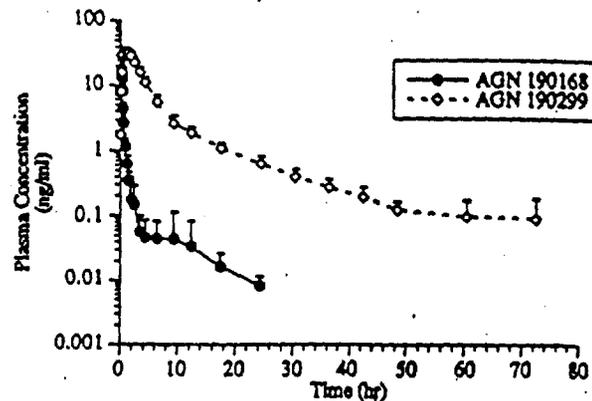


Figure 9.2.2

Plasma Concentration Versus Time Profiles of AGN 190168 and AGN 190299 Following a Single Intravenous Infusion Administration of AGN 190168 0.01% w/v Solution to Eight Healthy Subjects: Logarithmic Plot (Mean \pm S.D.). Lower figure is expansion of upper figure.

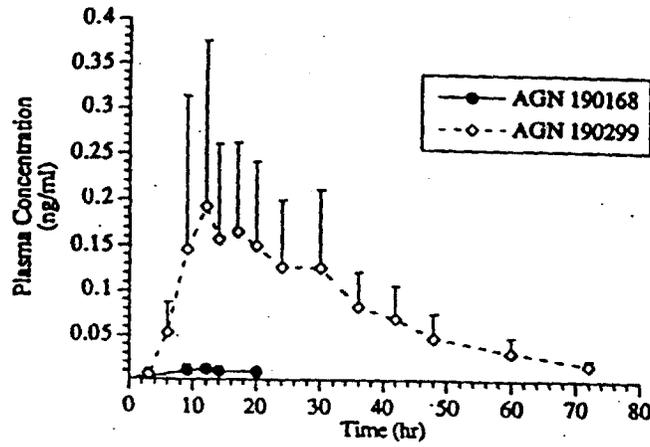


Figure 9.2.3 Plasma Concentration Versus Time Profiles of AGN 190168 and AGN 190299 Following a Single Topical Administration of AGN 190168 0.1% Gel to Eight Healthy Subjects: Linear Plot (Mean \pm S.D.)

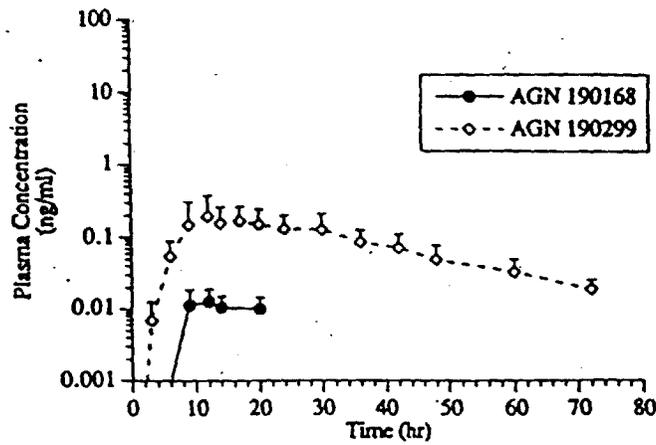


Figure 9.2.4 Plasma Concentration Versus Time Profiles of AGN 190168 and AGN 190299 Following a Single Topical Administration of AGN 190168 0.1% Gel to Eight Healthy Subjects: Logarithmic Plot (Mean \pm S.D.)

Table 9.1.6 Percentage of Dose Excreted into Urine Following a Single Intravenous Infusion and Single Topical Dose of AGN 190168 to Eight Healthy Subjects.

Intravenous Infusion Dose

		% Dose excreted		
Time	—	Mean	SD	CV%
hr		10.3	5.6	54.4
hr		1.09	1.01	92.0
hr		0.399	0.271	68.0
hr		0.0903	0.166	184
Total		11.9	5.23	43.9

Topical Administration

		% Dose excreted		
Time	—	Mean	SD	CV%
hr		0.0483	0.0653	1.35
hr		0.144	0.107	0.742
hr		0.115	0.0648	0.566
hr		0.0340	0.0189	0.556
Total		0.341	0.229	0.671

3%

Appendix 9.3.9 Listing of the Pharmacokinetic Parameters of AGN 190168 following a Single Intravenous Infusion Dose of AGN 190168 0.01% solution to Eight Healthy Subjects, by Subject with Summary Statistics.

Parameter (Unit)	Subject No.	Mean	S.D.	CV%	Min	Max
AUC ₀₋₂₄ (ng·hr/mL)		8.47	1.50	17.7	7.30	11.1
AUC _{0-TLDC} (ng·hr/mL)		7.28	2.17	29.8	3.59	11.1
AUC _{0-∞} (ng·hr/mL)		7.40	2.22	29.9	3.64	11.3
%AUC in terminal phase		17.3	30.48	174.4	3.3	92.5
k (hr ⁻¹)		0.111	0.0591	53.1	0.0226	0.200
t _{1/2} (hr)		6.22	3.52	56.6	3.46	30.7
Cl (L/hr)		161	50.8	31.5	98.2	275
Cl (L/hr/kg)		2.23	0.85	38.2	1.33	4.14
V _d (L)		1933	1194	61.8	701	4346
V _d (L/kg)		26.1	15.6	59.6	9.94	58.7
V _{ss} (L)		259	145	55.8	102	577
V _{ss} (L/kg)		3.55	2.08	58.8	1.65	8.18
AUMC _{0-TLDC} (ng·hr ² /mL)		8.68	7.63	87.9	2.32	26.3
AUMC _{0-∞} (ng·hr ² /mL)		13.5	9.39	69.6	3.13	31.0
MRT _{0-∞} ^{0.95} (hr)		1.73	1.09	62.9	0.633	4.11
MRT _{0-∞} ^{0.95} (hr)		1.56	1.09	69.6	0.467	3.94

NC = Not calculable

Appendix 9.3.12 Listing of the Pharmacokinetic Parameters of AGN 190299 following a Single Topical Dose of AGN 190168 0.1% gel to Eight Healthy Subjects, by Subject with Summary Statistics.

Parameter (Unit)	Subject No.	Mean	S.D.	CV%	Min	Max
C _{max} (ng/mL)		0.241	0.173	71.6	0.0420	0.576
t _{max} (hr)		18.6	6.05	32.5	12.0	30.0
AUC ₀₋₂₄ (ng·hr/mL)		2.78	1.85	66.6	0.702	5.74
AUC _{0-TLDC} (ng·hr/mL)		5.78	2.85	49.2	1.89	10.6
AUC _{0-∞} (ng·hr/mL)		6.25	2.87	46.0	2.27	11.2
k (hr ⁻¹)		0.0410	0.0072	17.5	0.0294	0.0497
t _{1/2} (hr)		16.9	2.95	17.4	14.0	23.6
F (% Dose)		0.550	0.219	39.8	0.255	0.850
AUMC _{0-TLDC} (ng·hr ² /mL)		162	75.0	46.4	60.9	317
AUMC _{0-∞} (ng·hr ² /mL)		207	81.0	39.2	102	376
MRT _{0-∞} ^{0.95} (hr)		35.0	7.00	20.0	24.3	44.8

Appendix 9.3.10 Listing of the Pharmacokinetic Parameters of AGN 190299 following a Single Intravenous Infusion Dose of AGN 190168 0.01% solution to Eight Healthy Subjects, by Subject with Summary Statistics.

Parameter (Unit)	Subject No.	Mean	S.D.	CV%	Min	Max
AUC ₀₋₂₄ (ng·hr/mL)		146	24.0	16.5	124	193
AUC _{0-TLDC} (ng·hr/mL)		156	25.0	16.1	129	204
AUC _{0-∞} (ng·hr/mL)		158	24.9	15.8	130	205
%AUC in terminal phase		20.8	5.48	26.3	14.3	31.7
k (hr ⁻¹)		0.0503	0.0081	16.2	0.0334	0.0615
t _{1/2} (hr)		13.8	2.19	15.9	11.3	20.7
Cl (L/hr)		7.11	0.961	13.5	6.05	8.84
Cl (L/hr/kg)		0.0970	0.0144	14.8	0.0732	0.115
V _d (L)		144	28.5	19.7	121	185
V _d (L/kg)		1.97	0.384	19.5	1.43	2.57
V _{ss} (L)		55.4	20.8	37.6	40.7	105
V _{ss} (L/kg)		0.750	0.244	32.5	0.483	1.27
AUMC _{0-TLDC} (ng·hr ² /mL)		1043	259	24.9	712	1394
AUMC _{0-∞} (ng·hr ² /mL)		1224	410	33.5	779	1995
MRT _{0-∞} ^{0.95} (hr)		7.76	2.39	30.8	5.98	13.0
MRT _{0-∞} ^{0.95} (hr)		6.20	2.44	39.4	4.47	11.8

Assuming Fm = 1

Appendix 9.3.11 Listing of the Pharmacokinetic Parameters of AGN 190168 following a Single Topical Dose of AGN 190168 0.1% gel to Eight Healthy Subjects, by Subject with Summary Statistics.

Parameter (Unit)	Subject No.	Mean	S.D.	CV%	Min	Max
C _{max} (ng/mL)		0.0160	0.0055	34.3	0.00652	0.0232
t _{max} (hr)		12.0	4.24	35.4	6.00	20.0
AUC ₀₋₂₄ (ng·hr/mL)		NC	NC	NC	NC	NC
AUC _{0-TLDC} (ng·hr/mL)		NC	NC	NC	NC	NC
AUC _{0-∞} (ng·hr/mL)		NC	NC	NC	NC	NC
k (hr ⁻¹)		NC	NC	NC	NC	NC
t _{1/2} (hr)		NC	NC	NC	NC	NC
F (% Dose)		NC	NC	NC	NC	NC
AUMC _{0-TLDC} (ng·hr ² /mL)		NC	NC	NC	NC	NC
AUMC _{0-∞} (ng·hr ² /mL)		NC	NC	NC	NC	NC
MRT _{0-∞} ^{0.95} (hr)		NC	NC	NC	NC	NC
MAT _{0-∞} ^{0.95} (hr)		28.8	8.54	29.7	12.5	40.1

NC = Not calculable

Listing of Plasma Concentration (ng/mL) versus Time of AGN 190168 following an Intravenous Infusion Dose of AGN 190168 into Eight Healthy Subjects over 20 Minutes, by Subject with Summary Statistics.

Time from end of infusion (hr)	Subject No.	Mean	S.D.	CV%	Min	Max
Pre-dose:		NC	NC	NC	0.00743	0.00743
-0.25		7.94	4.47	56.3	1.53	15.4
-0.166		13.3	5.99	45.1	5.44	23.9
-0.083		15.1	5.73	38.0	8.72	26.9
0		17.8	8.19	46.0	8.15	31.7
0.033		12.5	5.32	42.4	6.45	20.8
0.083		8.03	2.28	28.4	4.74	11.0
0.167		4.29	1.08	25.2	3.19	5.91
0.25		2.67	0.715	26.8	1.61	3.75
0.5		1.16	0.362	31.2	0.715	1.90
0.75		0.628	0.234	37.3	0.312	1.10
1		0.345	0.136	39.4	0.153	0.619
1.5		0.176	0.113	64.3	0.0570	0.407
2		0.147	0.142	96.3	0.0336	0.402
3		0.0566	0.0434	76.6	0.0137	0.126
4		0.0451	0.0406	90.1	0.0147	0.131
6		0.0443	0.0365	82.3	0.0100	0.110
9		0.0435	0.0709	163	0.00779	0.217
12		0.0332	0.0495	149	0.00691	0.142
17		0.0163	0.0100	61.3	0.00608	0.0347
24		0.00822	0.00310	37.7	0.00541	0.0123
30		NC	NC	NC	0.00506	0.0262
36		NC	NC	NC	0.00683	0.00683
42		NC	NC	NC	0.0225	0.0225
48		NC	NC	NC	0.00599	0.00676
60		NC	NC	NC	0.00542	0.00903
72		NC	NC	NC	0.00593	0.00776

BLQ = Below limit of quantitation (0.005 ng/mL)

NC = Not calculable

Listing of Plasma Concentration versus Time of AGN 190168 following a Topical Dose of AGN 190168 0.1% gel to Eight Healthy Subjects, by Subject with Summary Statistics.

Time after dose application (hr)	Subject No.	Mean	S.D.	CV%	Min	Max
Pre-dose:		NC	NC	NC	0	0
3		NC	NC	NC	0.0107	0.0107
6		NC	NC	NC	0.0122	0.0135
9		0.0113	0.00697	61.8	0.00605	0.0232
12		0.0126	0.00619	49.3	0.00701	0.0215
14		0.0104	0.00452	43.6	0.00686	0.0194
17		NC	NC	NC	0.00658	0.00822
20		0.00992	0.00436	43.9	0.00504	0.0159
24		NC	NC	NC	0.00556	0.00608
30		NC	NC	NC	0.00544	0.0163
36		NC	NC	NC	0.00719	0.00719
42		NC	NC	NC	0.00624	0.00624
48		NC	NC	NC	0	0
60		NC	NC	NC	0.00610	0.00610
72		NC	NC	NC	0.00823	0.00823

BLQ = Below limit of quantitation (0.005 ng/mL)

NC = Not calculable

Listing of Plasma Concentration versus Time of AGN 190299 following an Intravenous Infusion Dose of AGN 190168 into Eight Healthy Subjects over 20 Minutes, by Subject with Summary Statistics.

Time from end of infusion (hr)	Subject No.	Mean	S.D.	CV%	Min	Max
Pre-dose:		NC	NC	NC	0	0
0.25		1.74	0.838	48.2	0.349	2.97
0.166		7.82	2.41	30.8	3.98	11.1
0.083		15.7	2.99	19.1	10.5	20.2
0		25.1	5.51	21.9	17.6	33.6
0.033		27.7	6.20	22.4	17.7	35.1
0.083		30.7	5.59	18.2	21.8	38.1
0.167		33.6	5.92	17.6	23.4	43.8
0.25		33.2	5.43	16.4	22.9	40.5
0.5		33.2	5.26	15.8	23.8	41.2
0.75		34.0	5.05	14.9	28.9	42.7
1		31.7	5.15	16.3	23.4	40.4
1.5		29.3	4.37	14.9	24.5	37.1
2		22.9	3.86	16.9	18.7	29.3
3		16.0	3.20	19.9	13.3	22.7
4		10.9	2.33	21.4	8.71	15.9
6		5.48	1.40	25.6	4.21	8.43
9		2.58	0.807	31.3	1.51	3.74
12		1.86	0.433	23.2	1.28	2.45
17		1.09	0.256	23.4	0.749	1.42
24		0.640	0.190	29.6	0.415	0.953
30		0.400	0.126	31.5	0.251	0.631
36		0.274	0.0951	34.8	0.165	0.452
42		0.195	0.0832	42.6	0.105	0.351
48		0.124	0.0439	35.4	0.0802	0.220
60		0.0992	0.0760	76.6	0.0439	0.243
72		0.0910	0.0954	105	0.0278	0.308

BLQ = Below limit of quantitation (0.005 ng/mL)

NC = Not calculable

Listing of Plasma Concentration versus Time of AGN 190299 following a Topical Dose of AGN 190168 0.1% gel to Eight Healthy Subjects, by Subject with Summary Statistics.

Time after dose application (hr)	Subject No.	Mean	S.D.	CV%	Min	Max
Pre-dose:		NC	NC	NC	0	0
3		0.00602	0.00573	95.2	0	0.0161
6		0.0542	0.0337	62.1	0.0183	0.116
9		0.147	0.167	114	0.0384	0.537
12		0.193	0.184	95.3	0.0381	0.576
14		0.158	0.103	65.3	0.0322	0.298
17		0.166	0.0967	58.2	0.0413	0.31
20		0.151	0.0917	60.9	0.0419	0.312
24		0.128	0.0731	57.3	0.042	0.285
30		0.127	0.0845	66.6	0.0388	0.287
36		0.0836	0.0384	46.0	0.0328	0.167
42		0.0701	0.0366	52.2	0.0279	0.151
48		0.0485	0.0270	55.7	0.0218	0.109
60		0.0326	0.0165	50.7	0.0164	0.0688
72		0.0186	0.00647	34.7	0.0113	0.0301

BLQ = Below limit of quantitation (0.005 ng/mL)

NC = Not calculable