CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19787/S002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 25 1998

Clinical Pharmacology/Biopharmaceutics Review

NDA: 19-787 B002
Letter Date: July 11th, 1996
Drug: Amlodipine besylate (Norvasc)
Sponsor: Pfizer

Reviewer: Nakissa Sadrieh Ph.D.

Re: "A single blind, parallel group study of the effects of single and multiple doses of amlodipine, lisinopril, diltiazem and simvastatin on the pharmacokinetics of alcohol in normal volunteers." Protocol 053-016 study report.

Background:

It has been reported that a patient who was taking a combination of lisinopril, amlodipine and simvastatin (20 mg daily), exhibited very high blood alcohol levels suggestive of a drug interaction. It was however not clear which of the drugs the patient was taking was responsible for the interaction with alcohol, since there have been no previous interaction studies with alcohol, involving any of these drugs. Additionally, it has been reported that verapamil inhibits ethanol elimination in man.

Amlodipine is a calcium channel blocker of the 1,4-dihydropyridine family. It is approved in the US for the treatment of angina pectoris and mild to moderate essential hypertension.

Lisinopril is a synthetic peptide derivative long-acting angiotensin converting enzyme inhibitor that lowers blood pressure by inhibiting the renin-angiotensin-aldosterone system. Lisinopril is excreted unchanged in the urine. It is approved for the treatment of hypertension in the US.

Simvastatin is a methylated derivative of lovastatin which is a cholesterol lowering agent. It consists of a lactone which is hydrolyzed in vivo to its major active ß-hydroxyacid metabolite, an HMG-CoA reductase inhibitor. Simvastatin undergoes extensive hepatic first pass metabolism where its active metabolite is preferentially concentrated. It is approved in the US to treat hypercholesterolemia.

Diltiazem is a benzothiazepin derivative calcium channel blocker approved in the US for the treatment of hypertension and angina pectoris. Diltiazem has a short elimination

t ½ thus necessitating frequent dosing in man. However, upon increased dosing, the terminal t ½ increases, due to the non-linear PK characteristics of the drug. Diltiazem is extensively metabolized by CYP 3A and its major metabolite (N-demethydiltiazem) has pharmacological activity in man. Diltiazem is a competitive inhibitor of cyclosporine and propranolol.

The present study is aimed at reproducing the reported effect using amlodipine, lisinopril and simvastatin administered at a single dose and as multiple doses. Additionally, the effects of single and multiple doses of amlodipine and diltiazem are studied on the disposition of ethanol.

Results:

The pharmacokinetic parameters for ethanol are summarized in table 4.1.5 and the PK parameters for amlodipine are summarized in table 4.1.6.

The full model ANOVA indicated that there were no significant treatment group, period, or group*period interaction effects for ethanol AUC (0-8), Cmax or Tmax. When compared to baseline (placebo followed by ethanol), only single dose administration of diltiazem (120 mg) followed by ethanol ingestion resulted in a statistically higher mean AUC(0-8) estimate versus that obtained with single dose amlodipine (10 mg) and ethanol.

For amlodipine, no significant differences were noted between the 7-day and 15-day estimates. Mean systemic exposure to S- amlodipine was greater than that for R-amlodipine following multiple dose treatment by approximately 20% for both the amlodipine and combination treatment groups. Mean exposure of both enantiomers following single dose treatment was similar between the groups. The S-:R- ratio was generally 1.0 on day 7 and 1.2 on day 15 for both Cmax and AUC(0-12). The amlodipine S-:R- AUC(0-12) ratio was plotted against the ethanol AUC(0-8) for the combination and amlodipine groups for both the single and multiple dose groups. No relationship was apparent.

None of the treatment groups were significantly different from placebo in their effect on supine blood pressure, diastolic blood pressure and pulse.

After both single dosing (day 7) and multiple dosing (day 15), the drowsiness and intoxication scale scores of subjects treated with either amlodipine or with combination treatment, tended to decrease from baseline. The mean percentage changes from baseline in total intoxication score over time for subjects treated with amlodipine were –11% and –23% for single and multiple dosing, respectively. For the subjects treated with the combination of drugs, the percentage change from baseline in the intoxication score was –8% and –17% following single and multiple dosing, respectively.

The mean percentage changes from baseline in total drowsiness score over time for subjects treated with amlodipine were approximately –4% following both single and multiple dosing. For the subjects treated with the combination, the mean percent change in the drowsiness score over time was approximately 1% following both single and multiple dosing. However, none of the changes in score were significantly different from those observed in subjects treated with placebo.

Subjects treated with diltiazem had increases in intoxication and drowsiness scores above baseline following single and multiple dosing. However, the only differences relative to placebo that were statistically significant were in total drowsiness score over time after both single and multiple dosing (12% and 15%, respectively).

When compared to amlodipine or combination treatment, the intoxication scores for the diltiazem group were significantly higher following multiple dosing and the drowsiness scores for the diltiazem group were significantly higher for both single and multiple dosings. *This data is in accordance with the finding that diltiazem treatment followed by ethanol resulted in higher AUC for ethanol as compared to amlodipine treatment followed by ethanol treatment.*

It is concluded that there is no effect of amlodipine either alone or in combination with simvastatin and lisinopril on the PK of ethanol in healthy male volunteers.

Comments: These results do not provide additional information which could be included in the package insert.

Recommendations: No further action is recommended at this time.

/S/ 6/25/98

Nakissa Sadrieh. Ph.D.

RD/FT initialed by Patrick Marroum, Ph.D. /S/ 5/25/1998

cc: NDA19-787, HFD-110 (Roeder), HFD-860 (Sadrieh), CDER document room

Appendix 1

A single blind, parallel group study of the effects of single and multiple doses of amlodipine, lisinopril, diltiazem and simvastatin on the pharmacokinetics of alcohol in normal volunteers.

Study No. 053-016 **Volume 1.1-2** **Pages 1-771**

Study initiated April 26th, 1993
Study completed June 28th, 1993

Investigators:

Objectives:

1. To investigate the effect of single and multiple doses of amlodipine on the PK of ethanol.
2. To assess the effect of single and multiple doses of diltiazem on the PK of ethanol.
3. To evaluate the effect of co-administration of a combination of single and multiple doses of amlodipine, lisinopril and simvastatin on the PK of ethanol.
4. To examine the effect of these interactions on some simple measures of psychological evaluation (self-rated intoxication and drowsiness score).

Medication and dose level:

Amlodipine 10 mg tablets (FID #WW-89-018, lot number ED-G-014-190)
Diltiazem 120 mg tablets (lot number ED-0-44-293)
Lisinopril 20 mg tablets (lot number ED-0-043-293)
Simvastatin 40 mg tablets (lot number ED-0-042-293)
Matching placebo tablets (FID #QC 1657, lot number CO215-QC1567)

Study population:

Healthy male volunteers between the ages of 21 and 45 years with social drinking habits (less than or equal to 2 alcoholic beverages per day). Ten males are included in each group. Three subjects dropped out from the placebo group, but were replaced with other subjects.

Design:

This was a placebo-controlled, single-blind, randomized, parallel group study of single and multiple doses of amlodipine, either alone or in combination with simvastatin and lisinopril. Subjects were assigned to one of 4 treatment groups:

Group A: combination treatment (amlodipine 10 mg, lisinopril 20 mg, simvastatin 40 mg) once daily.
Group B: placebo 3 times daily.
Group C: amlodipine 10 mg once daily.
Group D: diltiazem 120 mg 3 times daily.

On day 1, all subjects were to take 1 placebo tablet at 7:00 and then ingest a single dose of ethanol (0.8 g/kg) 2 hours later.

On days 2-6, all subjects were to take 1 placebo tablet in the morning.

On day 7 (single dose assessment), subjects were to receive a single dose according to their group randomization at 7:00 am, and were then to ingest a single dose of ethanol 2 hours later.

On days 8-14, subjects were to receive study drug.

On day 15 (multiple dose assessment), subjects were to receive the morning dose as on days 8-14, and were to ingest a single dose of ethanol 2 hours later.

Please refer to the scheme of the study design which is enclosed in attachment 1.

Subjects were fasted for 8 hours prior to drug administration and for 4 hours following drug administration. A standard meal was to be served subsequently (composition not described). Study drug or placebo were administered with 240 ml water and ethanol was supplied as a 20% solution in orange juice.

Pharmacokinetic sampling:

Venous blood specimens were obtained for ethanol pharmacokinetic studies at the following time points:

> 2 hours pre-dose, just prior to dosing, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hours after dosing on days 1, 7 and 15.

Additionally, blood was also collected from the subjects in group A (combination) and group C (amlodipine) for the determination of plasma amlodipine levels. Sampling was done at the following time points:

Immediately prior to dosing, 2, 3, 4, 6, 8, 10, 12, 14, 18 and 26 hours after amlodipine administration on days 7 and 15.

Pharmacodynamic measures were to be based on changes in supine blood pressure and heart rate. Subjective psychological performance was to be assessed by means of a Visual Analogue Scale and a Drowsiness scale administered on days 1, 7 and 15.

Assay procedures:

Data analysis:

The concentrations of ethanol were quantifiable (2.8 μg/ml or greater) out to only 8 hours post ethanol ingestion, therefore the AUC (0-8 hours) was determined. The AUC (0-12 hours) was determined for R- and S- amlodipine. Cmax and Tmax were also determined.

Statistical analysis using ANOVA was performed to test for an overall period effect between days 1, 7 and 15 for ethanol AUC, Cmax and Tmax.

Results:

The pharmacokinetic parameters for ethanol are summarized in table 4.1.5 and the PK parameters for amlodipine are summarized in table 4.1.6. Additionally, please find enclosed a copy of the plasma concentration time profiles.

The full model ANOVA indicated that there were no significant treatment group, period, or group*period interaction effects for ethanol AUC (0-8), Cmax or Tmax. When compared to baseline (placebo followed by ethanol), only single dose administration of diltiazem (120 mg) followed by ethanol ingestion resulted in a statistically higher mean AUC(0-8) estimate versus that obtained with single dose amlodipine (10 mg) and ethanol.

For amlodipine, no significant differences were noted between the 7-day and 15-day estimates. Mean systemic exposure to S- amlodipine was greater than that for R-amlodipine following multiple dose treatment by approximately 20% for both the amlodipine and combination treatment groups. Mean exposure of both enantiomers following single dose treatment was similar between the groups. The S-:R- ratio was generally 1.0 on day 7 and 1.2 on day 15 for both Cmax and AUC(0-12). The amlodipine S-:R- AUC(0-12) ratio was plotted against the ethanol AUC(0-8) for the combination and amlodipine groups for both the single and multiple dose groups. No relationship was apparent.

None of the treatment groups were significantly different from placebo in their effect on supine blood pressure, diastolic blood pressure and pulse.

After both single dosing (day 7) and multiple dosing (day 15), the drowsiness and intoxication scale scores of subjects treated with either amlodipine or with combination treatment, tended to decrease from baseline. The mean percentage changes from baseline in total intoxication score over time for subjects treated with amlodipine were -11% and -23% for single and multiple dosing, respectively. For the subjects treated with the combination of drugs, the percentage change from baseline in the intoxication score was -8% and -17% following single and multiple dosing, respectively.

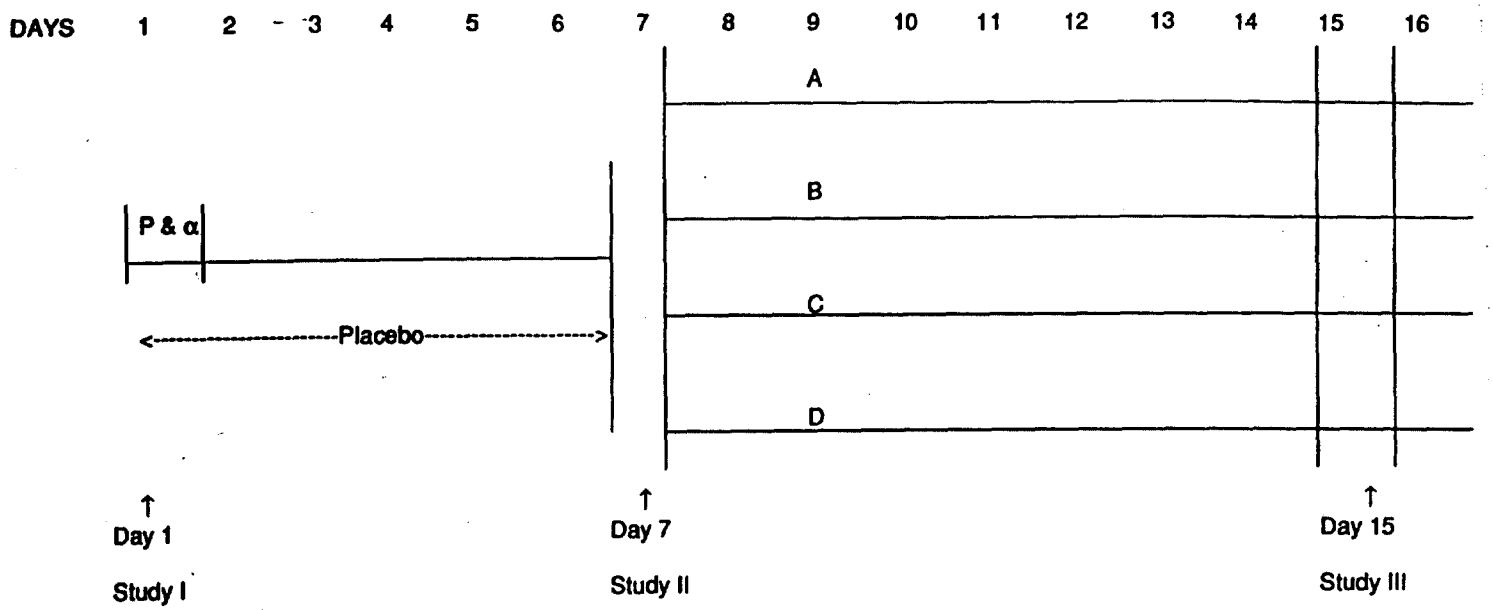
The mean percentage changes from baseline in total drowsiness score over time for subjects treated with amlodipine were approximately -4% following both single and multiple dosing. For the subjects treated with the combination, the mean percent change in the drowsiness score over time was approximately 1% following both single and multiple dosing. However, none of the changes in score were significantly different from those observed in subjects treated with placebo.

Subjects treated with diltiazem had increases in intoxication and drowsiness scores above baseline following single and multiple dosing. However, the only differences relative to placebo that were statistically significant were in total drowsiness score over time after both single and multiple dosing (12% and 15%, respectively).

When compared to amlodipine or combination treatment, the intoxication scores for the diltiazem group were significantly higher following multiple dosing and the drowsiness scores for the diltiazem group were significantly higher for both single and multiple dosings. *This data is in accordance with the finding that diltiazem treatment followed by ethanol resulted in higher AUC for ethanol as compared to amlodipine treatment followed by ethanol treatment.*

It is concluded that there is no effect of amlodipine either alone or in combination with simvastatin and lisinopril on the PK of ethanol in healthy male volunteers.

Attachment # 1
(Study Scheme)



Treatments

A = amlodipine, lisinopril, simvastatin

= placebo

C = amlodipine

D = diltiazem

P & α = placebo and alcohol

Table 4.1.5. Summary of Ethanol Pharmacokinetic Estimates Following Single Oral Doses of a 20% Ethanol Solution (0.8 g/kg) Ingested After Placebo (Day 1), and Single (Day 7) and Multiple (Day 15) Oral Doses of the Respective Treatments in Healthy Male Volunteers.
(Clinical Study # 053-016-599,

Treatment Group[a]	Day[b]	N	AUC(0-8) (µg•h/ml) Arithmetic Mean (SD)	AUC(0-8) (µg•h/ml) Geometric Mean	Cmax (µg/ml) Arithmetic Mean (SD)	Cmax (µg/ml) Geometric Mean	Tmax (h)
A	1	10	3980 (665)	3925	1001.5 (173.4)	986.3	1.4 (0.5)
	7	10	4246 (655)	4200	1089.2 (162.5)	1077.4	1.3 (0.5)
	15	10	4227 (720)	4173	1078.0 (151.8)	1068.4	1.2 (0.4)
B	1	10	4164 (907)	4069	1029.3 (193.8)	1012.5	1.4 (0.4)
	7	10	4292 (722)	4236	1080.6 (162.8)	1069.5	1.2 (0.5)
	15	10	4225 (801)	4150	1063.0 (148.0)	1053.3	1.1 (0.3)
C	1	10	4314 (629)	4269	1051.1 (107.1)	1046.1	1.2 (0.4)
	7	10	4335 (560)	4301	1080.2 (149.1)	1070.9	1.2 (0.5)
	15	10	4534 (976)	4448	1139.6 (132.8)	1133.1	1.0 (0.3)
D	1	10	3948 (569)	3913	982.1 (126.9)	974.3	1.5 (0.5)
	7	10	4482 (558)	4452	1042.6 (87.3)	1039.3	1.4 (0.7)
	15	10	4167 (554)	4122	1063.2 (160.8)	1034.2	1.7 (0.6)

[a]A = Amlodipine 10 mg qd, Lisinopril 20 mg qd, Simvastatin 40 mg qd
B = Placebo tid
C = Amlodipine 10 mg qd
D = Diltiazem 120 mg tid

[b]Day 1 = Placebo administration to all subjects in all treatment groups followed by ethanol 2 hours post placebo
Day 7 = Single dose administration followed by ethanol at 2 hours post-dose.
Day 15 = Multiple dose administration (i.e., from Day 8) followed by ethanol at 2 hours post-dose.

Table 4.1.6. Summary of R(+) and S(-)-Amlodipine Pharmacokinetic Estimates Following Single (Day 7) and Multiple Doses (Day 15) of the Respective Treatments and a Single Oral Dose of a 20% Ethanol Solution (0.8 g/kg) In Healthy Male Subjects. (Clinical Study # 053-016-599,

Treatment Group[a]	Day[b]	N		AUC(0-12) (µg•h/ml)		Cmax (µg/ml)		Tmax (h)		S(-):R(+)	
				R(+)	S(-)	R(+)	S(-)	R(+)	S(-)	AUC(0-12)	Cmax
A	7	10	Arithmetic Mean	20.2	20.1	2.39	2.40	8.8	9.2	1.006	1.005
			(SD)	7.1	6.6	0.75	0.73	1.7	1.9	0.083	0.066
			Geometric Mean	19.0	19.0	2.28	2.29	--	--	1.003	1.003
A	15	10	Arithmetic Mean	69.7	80.9	6.97	8.34	7.0	7.4	1.192	1.237
			(SD)	28.3	29.2	2.75	2.6	2.2	1.9	0.274	0.231
			Geometric Mean	64.6	75.2	6.5	7.92	--	--	1.164	1.218
C	7	9	Arithmetic Mean	19.0	19.4	2.27	2.30	6.7	6.2	1.031	1.017
			(SD)	5.8	5.0	0.70	0.65	2.0	2.1	0.064	0.054
			Geometric Mean	18.3	18.8	2.18	2.22	--	--	1.029	1.015
C	15	10	Arithmetic Mean	72.7	89.5	6.99	8.85	7.8	8.8	1.250	1.278
			(SD)	22.3	26.5	2.02	2.66	3.0	2.5	0.170	0.170
			Geometric Mean	69.2	85.8	6.68	8.47	--	--	1.240	1.268

[a]A = Amlodipine 10 mg qd, Lisinopril 20 mg qd, Simvastatin 40 mg qd
C = Amlodipine 10 mg qd

[b]Day 7 = Single dose administration followed by ethanol at 2 hours postdose.
Day 15 = Multiple dose administration (i.e., from Day 8) followed by ethanol at 2 hours postdose.

Figure 13. Mean Ethanol Plasma Concentrations Following Ingestion of a Single Oral Dose of a 20% Ethanol Solution (0.8 g/kg) at 2 Hours After Administration of a Single Oral Dose of Placebo (Day 1), and Single (Day 7) and Multiple (Day 15) Daily Oral Doses of Amlodipine 10 mg, Lisinopril 20 mg, and Simvastatin 40 mg to the Healthy Male Subjects in Group A
(Clinical Study #053-016-599,)

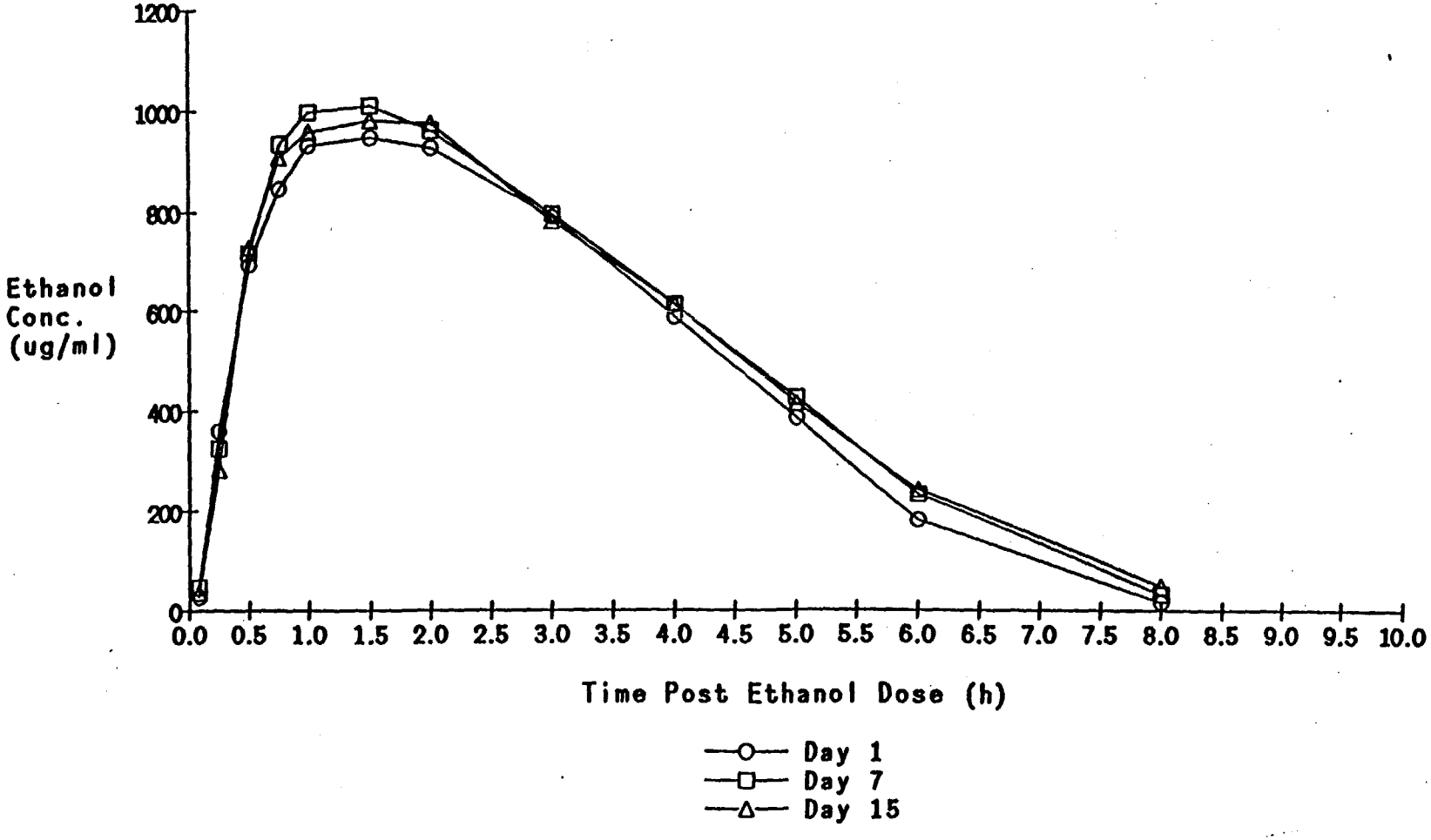


Figure 14. Mean Ethanol Plasma Concentrations Following Ingestion of a Single Oral Dose of a 20% Ethanol Solution (0.8 g/kg) at 2 Hours After Administration of a Single Oral Dose of Placebo (Day 1), and Single (Day 7) and Multiple (Day 15) Daily Oral Doses of Placebo to the Healthy Male Subjects in Group B
(Clinical Study #053-016-599,)

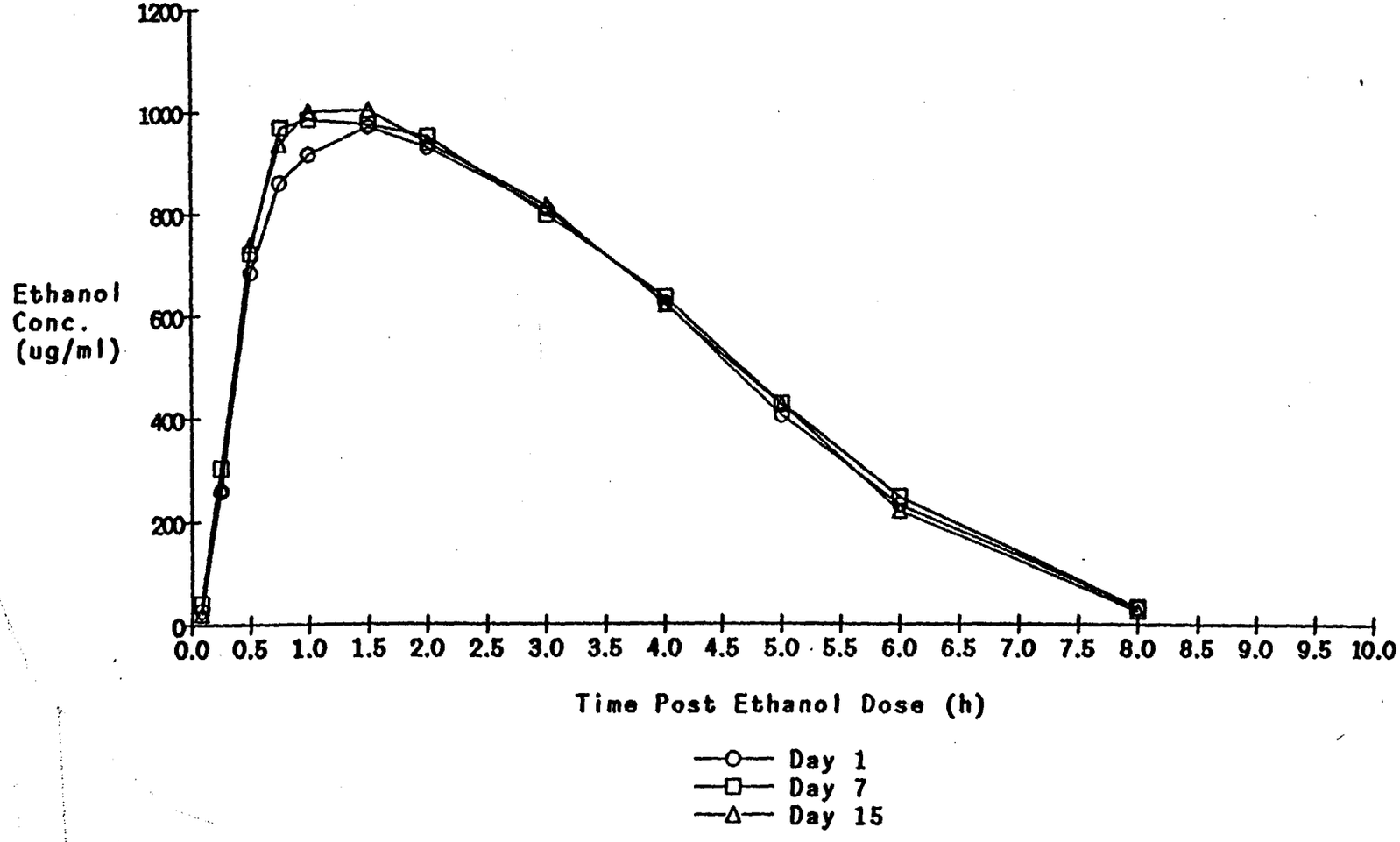


Figure 15. Mean Ethanol Plasma Concentrations Following Ingestion of a Single Oral Dose of a 20% Ethanol Solution (0.8 g/kg) at 2 Hours After Administration of a Single Oral Dose of Placebo (Day 1), and Single (Day 7) and Multiple (Day 15) Daily Oral Doses of Amlodipine 10 mg to the Healthy Male Subjects in Group C
(Clinical Study #053-016-599,)

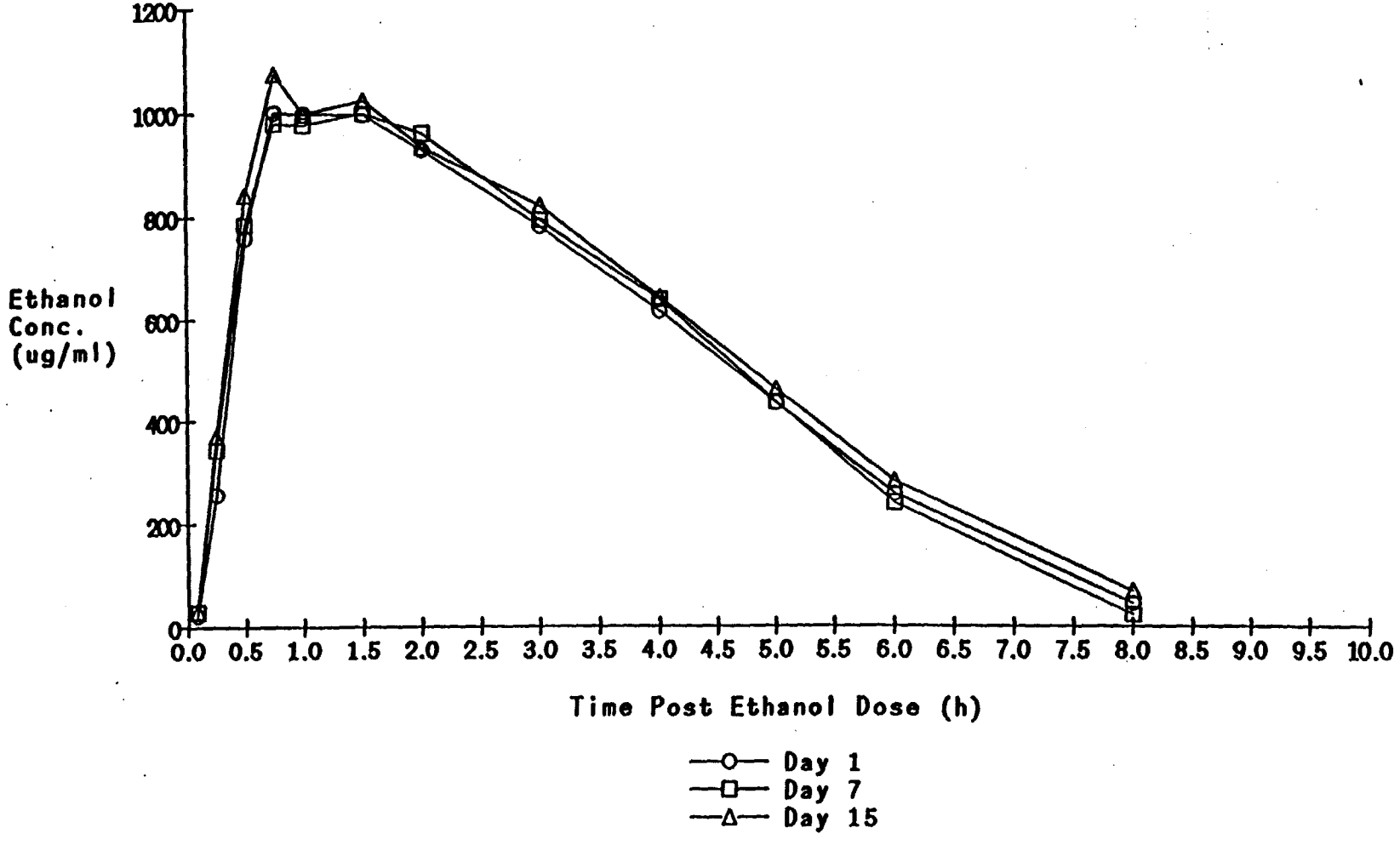


Figure 16. Mean Ethanol Plasma Concentrations Following Ingestion of a Single Oral Dose of a 20% Ethanol Solution (0.8 g/kg) at 2 Hours After Administration of a Single Oral Dose of Placebo (Day 1), and Single (Day 7) and Multiple (Day 15) Oral Doses of Diltiazem 120 mg to the Healthy Male Subjects in Group D (Clinical Study #053-016-599,)

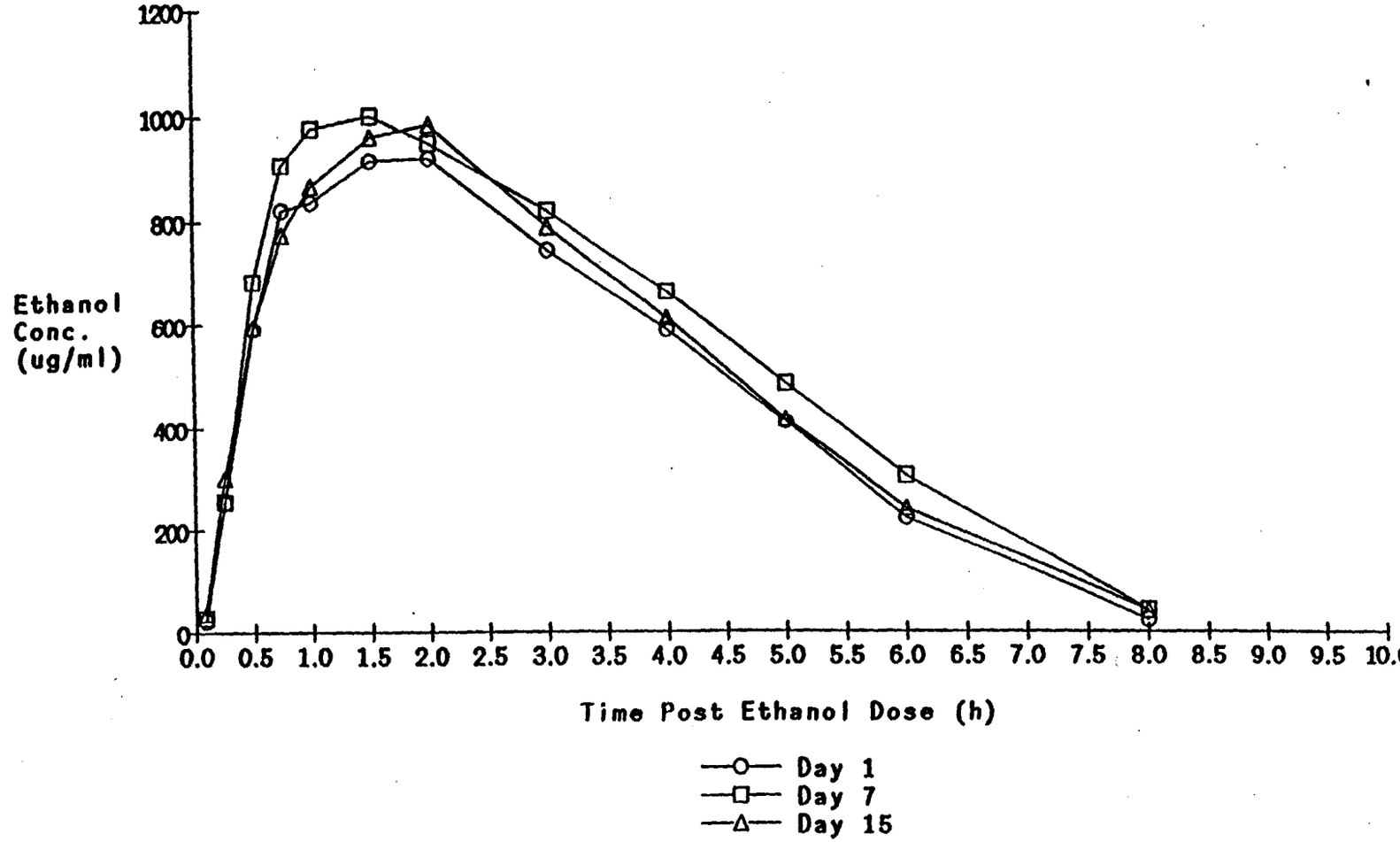


Figure 25. Mean Amlodipine Enantiomer Concentrations Following Ingestion of a 20% Ethanol Solution at 2 Hours After Single (Day 7) and Multiple (Day 15) Doses of Amlodipine 10 mg, Lisinopril 20 mg, Simvastatin 40 mg to Healthy Male Subjects (Group A)

(Clinical Study #053-016-599,)

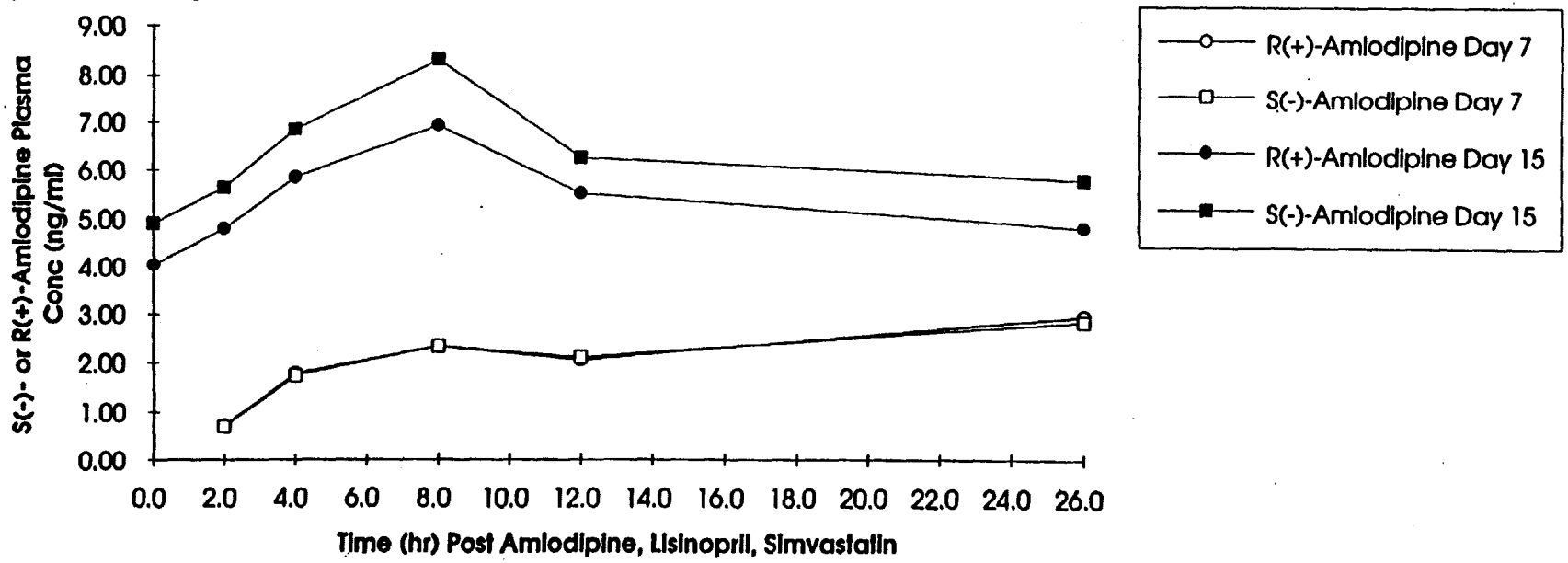


Figure 26. Mean Amlodipine Enantiomer Concentrations Following Ingestion of a 20% Ethanol Solution at 2 Hours After Single (Day 7) and Multiple (Day 15) Doses of Amlodipine 10 mg to Healthy Male Subjects (Group C) (Clinical Study #053-016-599,)