

2966 01 SEP 20 09:41

WRITER'S DIRECT ACCESS

September 20, 2001

John B. Dubeck
(202) 434-4125
dubeck@khlaw.com

Via Messenger

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 00P-1199; Supplement to Citizen Petition Concerning Bioequivalence Determinations for Extended-Release Drug Products

Dear Sir or Madam:

On behalf of our client, Biovail Corporation, we are hereby submitting additional information to supplement Citizen Petition 00P-1199 (submitted March 16, 2000).¹ In the original Petition, Biovail questioned the validity of the practice of the Office of Generic Drugs to grant bioequivalence waivers for lower dosage strength formulations of a certain category of extended-release drug products: Those formulations that depend upon a blend of a limited number of bead types with different dissolution characteristics to achieve the desired extended-release profile. The Petition requested that the Commissioner refrain from granting approval to Abbreviated New Drug Applications (ANDAs) for extended-release generic drugs consisting of a blend of a small number of different types of beads containing active ingredients with intentionally different release characteristics unless bioequivalence has been demonstrated for both the highest and lowest dose form of the product, or until alternate methods are available to assure that a demonstration of bioequivalence at one dose will assure bioequivalence at all other doses. The Petition also urged FDA to reevaluate previously issued approvals and, as necessary, request additional data to ensure that all generic doses are bioequivalent to the corresponding dose for the reference listed drug (RLD). The enclosed data demonstrate that a currently marketed product of the type described by the Petition is not bioequivalent.

¹ On September 5, 2000, FDA responded that "[b]ecause of the complexity of the issues raised in the petition, work on the petition is still in progress." Biovail has received no further word from FDA since this time.

00P-1199

Sup1

As noted in Biovail's original petition, the concern with regard to lower dosage strengths is related to difficulties involved in establishing blend uniformity. In August 1999, FDA released a draft document and sought comment with respect to "Guidance for Industry - ANDAs: Blend Uniformity Analysis" ("BUA Guidance"). Biovail pointed out some shortcomings of that guidance with regard to the extended release drugs that were the subject of the petition, including the inadequacy of using an analytical method that simply checked the blend for the amount of active ingredient present. All of the beads in a formulation consisting of a blend of beads with intentionally different dissolution rates contain active ingredient. An effective BUA for such a product would need to characterize the relative proportion of each bead type for a sample size corresponding to the lowest dosage strength. Absent such analytical evidence of uniformity at the lower dosage strengths, there can be no assurance that the lower strength dosage forms will behave similarly to the highest strength dosage forms that were actually studied for bioequivalence unless the bioequivalence of the lower strength dosage forms is directly tested.

Biovail neither has access to bulk quantities of raw batches of blended bead populations used in competitive drug products nor to manufacturing specifications for such products, so it is not possible for Biovail to directly determine whether the manufacture of such products is supported by adequate blend uniformity data. Like the hypertensive patients that depend upon extended-release diltiazem drug products, however, Biovail does have access to commercially marketed products containing diltiazem in which the extended-release properties are the result of blending beads with intentionally different dissolution specifications.

Biovail has sponsored, and is hereby submitting, clear evidence that a commercially available product of the type described by the Petition is not, in fact bioequivalent to the RLD. Cartia XT^{TM2} (Andrx Pharmaceuticals) is represented to be bioequivalent to Cardizem® CD (the RLD) (Biovail Corporation³). Enclosed are the first 398 pages of Volume 1 (Summary, Report, and Tables and Figures) of a study entitled "Two-Way Cross-over Single-Dose Open-Label Fasting Pharmacokinetic Study of Cartia XTTM 300 mg Capsules Versus Cardizem® CD 300 mg

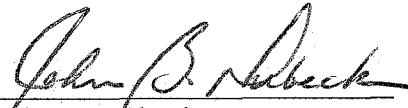
² The two bead character of Cartia XTTM is amply documented by Andrx's own public filings with FDA. See Docket 98P-0145 (Andrx contending that any generic versions of Cardizem® CD be required to demonstrate the "two peak" profile of the RLD, even if other bioequivalence criteria are satisfied).

³ Cardizem® CD was originally developed and shepherded through the FDA approval process by corporate predecessors to Aventis. As of January 2001, Biovail purchased the entire Cardizem franchise from Aventis and thus steps into its shoes with respect Cardizem® CD.

Capsules, in Normal Healthy Non-Smoking Male Subjects.”⁴ The study compares the 300 mg⁵ strengths of Cardizem® CD and Cartia XT™ diltiazem hydrochloride extended-release capsules. The Cartia XT™ product was found to fall outside FDA’s criteria for bioequivalence with regard to C_{max} (80 – 125%); for Cartia XT™, the 90% geometric confidence interval for C_{max} was 73.84%-89.37%. Patients titrated for blood pressure maintenance with the lower C_{max} of the Cartia XT™ product would be at risk of dangerously low blood pressure if their next prescription refill were with the RLD or a generic that was bioequivalent to the RLD.

The enclosed study report confirms that the concerns expressed in the original Petition are far from idle speculation, but represent a serious risk to public health. FDA must act to correct this situation immediately.

Respectfully submitted,


John B. Dubeck

Keller and Heckman LLP
1001 G Street, NW, Suite 500W
Washington, DC 20001
Ph: 202-434-4200

Counsel to Biovail Corporation

Enclosures

⁴ Study # 2443 (B01-527PK-FILG12). The full study report (5 volumes) is being submitted under separate cover to the Office of Generic Drugs for its consideration.

⁵ This is the highest approved dosage strength for Cartia XT™ and it presumably was the subject of bioequivalence testing prior to approval. The fact that the commercial distribution of the highest dosage strength is not bioequivalent underscores the BUA issues raised in the original petition and the alternative relief sought that FDA withhold approvals “until alternate methods are available to assure that a demonstration of bioequivalence at one dose will assure bioequivalence at all other doses.” It would appear that in the absence of an effective BUA protocol specific to these types of dosage formulations there may be a lack of assurance that even a single dosage strength will continue to be bioequivalent from one batch to the next.



BIOVAIL
CONTRACT RESEARCH

STUDY # 2443 (B01-527PK-DILG12)

**A TWO-WAY CROSS-OVER SINGLE-DOSE OPEN-LABEL FASTING
PHARMACOKINETIC STUDY OF CARTIA XTTM 300 mg CAPSULES VERSUS
CARDIZEM[®] CD 300 mg CAPSULES, IN NORMAL HEALTHY NON-SMOKING MALE
SUBJECTS**

VOLUME I OF V

for

**BIOVAIL CORPORATION
c/o BIOVAIL TECHNOLOGIES LIMITED
3701 Concorde Parkway, Suite 800
Chantilly, VA 20151
U.S.A.**

by

**BIOVAIL CONTRACT RESEARCH
a Division of
BIOVAIL CORPORATION
460 Comstock Road
Toronto, Ontario
Canada M1L 4S4**

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
460 Comstock Road, Toronto, Ontario, Canada M1L 4S4
Tel: (416) 752-3636 / 1-888-240-8245 Fax: (416) 752-7610



BIOVAIL
CONTRACT RESEARCH

STUDY # 2443 (B01-527PK-DILG12)


**A TWO-WAY CROSS-OVER SINGLE-DOSE OPEN-LABEL FASTING
PHARMACOKINETIC STUDY OF CARTIA XT™ 300 mg CAPSULES VERSUS
CARDIZEM® CD 300 mg CAPSULES, IN NORMAL HEALTHY NON-SMOKING MALE
SUBJECTS**

for

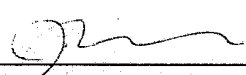
**BIOVAIL CORPORATION
c/o BIOVAIL TECHNOLOGIES LIMITED
3701 Concorde Parkway, Suite 800
Chantilly, VA 20151
U.S.A.**

by

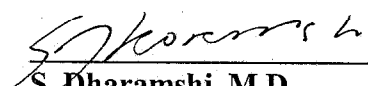
**BIOVAIL CONTRACT RESEARCH
a Division of
BIOVAIL CORPORATION
460 Comstock Road
Toronto, Ontario
Canada M1L 4S4**



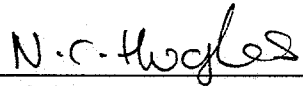
P. Y. Tam, M.D., F.R.C.P., F.A.C.P. Date: 07-13-2001
Medical Director (mm-dd-yyyy)
Principal Investigator

 / FOR

K. Sacramed, C.C.R.C. Date: 07-13-2001
Director of Bio Centre (mm-dd-yyyy)



S. Dharamshi, M.D. Date: 07-13-2001
Study Director (mm-dd-yyyy)



B. Matthews, B.Sc. Date: 07-13-2001
Director of Bioanalytical Lab. (mm-dd-yyyy)

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
460 Comstock Road, Toronto, Ontario, Canada M1L 4S4
Tel: (416) 752-3636 / 1-888-240-8245 Fax: (416) 752-7610



STUDY # 2443 (B01-527PK-DILG12)

**A TWO-WAY CROSS-OVER SINGLE-DOSE OPEN-LABEL FASTING
PHARMACOKINETIC STUDY OF CARTIA XT™ 300 mg CAPSULES VERSUS
CARDIZEM® CD 300 mg CAPSULES, IN NORMAL HEALTHY NON-SMOKING MALE
SUBJECTS**

Documentation

Prepared By:

S. Ramnarine 07-12-2001
S. Ramnarine, Hon.B.Sc. Date
Scientific Report Writer (mm-dd-yyyy)

Reviewed By:

C. Simmons 07-12-2001
C. Simmons, B.A. (Hons.) Date
Scientific Report Writer (mm-dd-yyyy)

G. LeBlanc 07-12-2001
G. LeBlanc, M.Sc. Date
Manager, (mm-dd-yyyy)
Document Control

Pharmacokinetic and Statistical Analysis

Prepared By:

H. Dong 07-13-2001
H. Dong, M.Sc. Date
Data Analyst (mm-dd-yyyy)

Reviewed By:

E. Edwards 07-12-2001
E. Edwards, Ph.D. Date
Manager, (mm-dd-yyyy)
Pharmacokinetics & Statistics

Clinic Records and Medical Records

Reviewed By:

D. Mitchell 07-12-2001
D. Mitchell, R.N. Date
Clinical Research Coordinator (mm-dd-yyyy)



QUALITY ASSURANCE STATEMENT

The following report has been reviewed and certain period(s) of the clinical study and/or analytical data generated relevant to this report have been inspected by Biovail Contract Research (BCR) Quality Assurance Unit in compliance with Good Laboratory and Clinical Practices and/or other appropriate regulations as well as BCR's applicable Standard Operating Procedures. Additional procedural inspections may have been done for this study and reports are archived within the QA Department files. The report accurately presents the raw data, statistical analysis generated (as required) and clinical/laboratory activities inspected for this study.

Study No.: 2443 (B01-527PK-DILG12)

Title: A Two-Way, Crossover, Single-Dose, Open-Label, Fasting Pharmacokinetic Study of Cartia XT™ 300 mg Capsules Versus Cardizem® CD 300 mg Capsules in Normal Healthy Non-Smoking Male Subjects

Sponsor: BIOVAIL CORPORATION
 c/o Biovail Technologies Limited
 3701 Concorde Parkway, Suite 800
 Chantilly, VA 20151
 U.S.A.

Inspection of	Inspection Date	Report Issued to Management	Inspector(s)	
			Name	Signature
Clinical Records <ul style="list-style-type: none"> • Pre-Study • Post-Study 	04-11, 12-2001	04-12-2001	H. Ma	<i>H. Ma</i>
	05-15, 16, 17, 18-2001	05-18-2001	A. Ama	<i>A. Ama</i>
			H. Ma	<i>H. Ma</i>
Analytical Data	05-22, 23, 25-2001	05-28-2001	I. Hashmi	<i>I. Hashmi</i>
Final Report	07-09, 10, 11, 12-2001	07-12-2001	E. Bass	<i>E. Bass</i>

E. Bass
 Quality Assurance Unit

07-13-2001
 Date (mm-dd-yyyy)

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvate transaminase)
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetate transaminase)
AUC	Area under the curve
BCR	Biovail Contract Research
C.I.	Confidence Interval
C_{max}	Peak plasma concentration
CV	Coefficient of Variation
ECG	Electrocardiogram
GLM	General Linear Models
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
K_{e1}	Elimination rate constant
N.C.	Not Calculated/No Calculation
N.D.	No Data
N.S.	No Sample
N.Q.	Not Quantifiable
PCP	Phencyclidine
SD	Standard Deviation
$t_{1/2}$	Half-life
T_{max}	Time to reach peak plasma concentration
Cardizem CD	Cardizem [®] CD
Cartia XT	Cartia XT [™]

TABLE OF CONTENTS

STUDY # 2443 (B01-527PK-DILG12)

**A TWO-WAY CROSS-OVER SINGLE-DOSE OPEN-LABEL FASTING
PHARMACOKINETIC STUDY OF CARTIA XT™ 300 mg CAPSULES VERSUS
CARDIZEM® CD 300 mg CAPSULES, IN NORMAL HEALTHY NON-SMOKING
MALE SUBJECTS**

VOLUME I OF V	PAGE NUMBER
SUMMARY	
Investigators and Facilities	001
Executive Summary	002
Summary of Results	003
REPORT	
Objective	012
Facilities	012
Protocol and Informed Consent	013
Study Drug Information	013
Procedures	014
Adverse Events	018
Protocol Deviations	019
Demographics Table	020
Dosage Regimen Table	021
Blood Sampling Time Deviations Table	022
Summary of Adverse Events.....	024
Pharmacokinetic and Statistical Analyses	026
Experimental Results	
Section 1.0: Plasma Diltiazem Data	
Plasma Diltiazem Concentrations	028
Pharmacokinetic Parameters for Each Subject	028
Area Under the Plasma Diltiazem Concentration-Time Curve (0-t hours)	028
Area Under the Plasma Diltiazem Concentration-Time Curve (0-infinity)	029
Peak Plasma Diltiazem Concentrations	030
Time to Reach Peak Plasma Diltiazem Concentrations	031
The Apparent Half-Life and Elimination Rate Constant of Plasma Diltiazem.....	031

TABLE OF CONTENTS

STUDY # 2443 (B01-527PK-DILG12)

A TWO-WAY CROSS-OVER SINGLE-DOSE OPEN-LABEL FASTING PHARMACOKINETIC STUDY OF CARTIA XT™ 300 mg CAPSULES VERSUS CARDIZEM® CD 300 mg CAPSULES, IN NORMAL HEALTHY NON-SMOKING MALE SUBJECTS

VOLUME I OF V (Cont'd)	PAGE NUMBER
Experimental Results (Cont'd)	
Section 2.0: Plasma Desacetyldiltiazem Data	
Plasma Desacetyldiltiazem Concentrations	033
Pharmacokinetic Parameters for Each Subject	033
Area Under the Plasma Desacetyldiltiazem Concentration-Time Curve (0-t hours)	033
Area Under the Plasma Desacetyldiltiazem Concentration-Time Curve (0-infinity)	034
Peak Plasma Desacetyldiltiazem Concentrations	035
Time to Reach Peak Plasma Desacetyldiltiazem Concentrations	036
The Apparent Half-Life and Elimination Rate Constant of Plasma Desacetyldiltiazem	036
Section 3.0: Plasma N-Desmethyldiltiazem Data	
Plasma N-Desmethyldiltiazem Concentrations	038
Pharmacokinetic Parameters for Each Subject	038
Area Under the Plasma N-Desmethyldiltiazem Concentration-Time Curve (0-t hours)	038
Area Under the Plasma N-Desmethyldiltiazem Concentration-Time Curve (0-infinity)	039
Peak Plasma N-Desmethyldiltiazem Concentrations	040
Time to Reach Peak Plasma N-Desmethyldiltiazem Concentrations	041
The Apparent Half-Life and Elimination Rate Constant of Plasma N-Desmethyldiltiazem	041
Conclusions	043

TABLE OF CONTENTS

STUDY # 2443 (B01-527PK-DILG12)

A TWO-WAY CROSS-OVER SINGLE-DOSE OPEN-LABEL FASTING PHARMACOKINETIC STUDY OF CARTIA XT™ 300 mg CAPSULES VERSUS CARDIZEM® CD 300 mg CAPSULES, IN NORMAL HEALTHY NON-SMOKING MALE SUBJECTS

VOLUME I OF V (Cont'd)	PAGE NUMBER
TABLES AND FIGURES	
Section 1.0: Plasma Diltiazem	
Tables	045
Figures	068
Section 2.0: Plasma Desacetyldiltiazem	
Tables	163
Figures	187
Section 3.0: Plasma N-Desmethyldiltiazem	
Tables	282
Figures	305

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
STUDY # 2443 (B01-527PK-DILG12)

INVESTIGATORS AND FACILITIES

TITLE: A Two-Way Cross-Over Single-Dose Open-Label Fasting Pharmacokinetic Study of Cartia XT™ 300 mg Capsules Versus Cardizem® CD 300 mg Capsules In Normal Healthy Non-Smoking Male Subjects
Study No. 2443 (B01-527PK-DILG12)

SPONSOR: BIOVAIL CORPORATION
c/o BIOVAIL TECHNOLOGIES LIMITED
3701 Concorde Parkway, Suite 800
Chantilly, VA 20151
U.S.A.

Sponsor Contact: Sury Sista, Ph.D.
Director of Pharmacokinetics
Telephone: (703) 995-2356, Fax: (703) 995-2490

REPORT ISSUER, CLINICAL, STATISTICAL, AND ANALYTICAL FACILITY: Biovail Contract Research
a Division of Biovail Corporation
460 Comstock Road/689 Warden Avenue Units 1 & 2
Toronto, Ontario, Canada M1L 4S4/M1L 4R6
Telephone: (416) 752-3636/(416) 686-6334
Fax: (416) 752-7610/(416) 690-1880

Medical Director and Principal Investigator: Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.
Study Director: Shafik Dharamshi, M.D.
Director of Bio Centre: Kcennia Sacramed, C.C.R.C.
Director of Bioanalytical Lab: Brent Matthews, B.Sc.

CLINICAL LABORATORY: Gamma-Dynacare Medical Laboratories
115 Midair Court
Brampton, Ontario, Canada L6T 5M3
Telephone: (905) 790-3000, Fax: (905) 790-3055
Medical Director: Shabnam Sethi Rajani, M.D.

NO. OF SUBJECTS: 27
STUDY DESIGN: Two-Way, Single-Dose, Fasting
CLINICAL STUDY DATES:
Dosing Dates: Period I: April 14, 2001; Period II: April 21, 2001;
Start - End Dates: April 13, 2001 to April 23, 2001

FORMULATIONS TESTED:

Treatment A: Cartia XT™ (diltiazem HCl extended release capsules, USP) 300 mg Capsules
Lot #: 600A073 ; Expiry Date: 07/02
(Andrx Pharmaceuticals, Inc.)

Treatment B: Cardizem® CD (diltiazem HCl) 300 mg Capsules
Lot #: 1030455; Expiry Date: 11/2002
(Aventis Pharmaceuticals, Inc.)

EXECUTIVE SUMMARY

This randomized, open-label, single-dose, two-way, crossover study was designed to evaluate the pharmacokinetics of the test product, Cartia XT™ (diltiazem HCl extended release capsules, USP) 300 mg Capsules (Andrx Pharmaceuticals, Inc.), versus the reference product, Cardizem® CD (diltiazem HCl) 300 mg Capsules (Aventis Pharmaceuticals, Inc.) under fasting conditions. The two study periods were separated by a one-week washout period. Twenty-three (23) blood samples were drawn for drug content analysis at 0.0 (pre-drug), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 18.0, 24.0, 30.0, 36.0, 42.0 and 48.0 hours post-drug administration during each study period. Upon completion of the clinical portion of the study, all plasma samples were delivered to the analytical facility for the determination of diltiazem, desacetyldiltiazem and N-desmethyl diltiazem concentrations. Twenty-eight (28) qualified subjects were entered into the study. Pharmacokinetic and statistical analyses were conducted on twenty-seven (27) evaluable subjects that completed the study. Eleven (11) subjects experienced a total of nineteen (19) adverse events during the study, consisting of headaches, nausea, loose stool, dizziness, vomiting, decreased glucose, elevated protein in urine, decreased neutrophil count, decreased WBC count, decreased calcium, leukocytes in urine, elevated glucose and elevated ALT. There were no protocol deviations and twenty-seven (27) blood sampling time deviations reported during the study.

The 90% geometric confidence intervals for diltiazem AUC_{0-t} , AUC_{0-inf} and C_{max} were 82.23 – 95.01%, 82.89 – 95.36% and 73.84 – 89.37%, respectively, with point estimates of 88.39%, 88.90% and 81.23% respectively. The test product therefore failed to demonstrate bioequivalence to the reference product. Metabolite data are provided as additional information.

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
STUDY # 2443 (B01-527PK-DILG12)

SUMMARY OF RESULTS

Section 1.0: Mean Pharmacokinetic Parameters for Plasma Diltiazem (n = 27)

Parameter	CARTIA XT™ (A) ¹	CARDIZEM® CD (B) ²
	Lot #: 600A073 Mean ± SD	Lot #: 1030455 Mean ± SD
AUC (0 - t) (ng · hr/mL)	2459.96 ± 1086.85	2818.93 ± 1350.22
AUC (0 - inf) (ng · hr/mL)	2583.31 ± 1151.26	2949.87 ± 1434.92
C _{max} (ng/mL)	121.29 ± 51.30	152.32 ± 70.88
T _{max} (hours)	11.22 ± 4.70	7.22 ± 4.41
t _{1/2} (hours)	8.11 ± 1.90	7.59 ± 1.24
K _{el} (hour ⁻¹)	0.089 ± 0.017	0.094 ± 0.015

CARTIA XT™ (A) vs. CARDIZEM® CD (B)

	AUC (0 - t)	AUC (0 - infinity)	C _{max}
90% Geometric CI. ³	82.23 % - 95.01 %	82.89 % - 95.36 %	73.84 % - 89.37 %
Ratio of Means ⁴	88.39 %	88.90 %	81.23 %
Intra-Subject C.V. ⁵	15.52 %	15.06 %	20.52 %

¹ One (1) Cartia XT™ (diltiazem HCl extended release capsules, USP) 300 mg Capsule (Andrx Pharmaceuticals, Inc.; Lot #: 600A073; Expiry Date: 07/02) (Total dose = 300 mg).

² One (1) Cardizem® CD (diltiazem HCl) 300 mg Capsule (Aventis Pharmaceuticals, Inc.; Lot #: 1030455; Expiry Date: 11/2002) (Total dose = 300 mg).

³ 90% Geometric Confidence Interval using log-transformed data and CARDIZEM® CD (B) as the reference (Aventis Pharmaceuticals, Inc.; Lot #: 1030455; Expiry Date: 11/2002), calculated based on two-way A vs. B comparison.

⁴ Calculated using geometric means according to the formula: $e^{(\text{CARTIA XT}^{\text{TM}}(\text{A}) - \text{CARDIZEM}^{\text{®}} \text{CD}(\text{B}))} \times 100\%$, calculated based on two-way A vs. B comparison.

⁵ Intra-subject coefficient of variation for log-transformed pharmacokinetic parameter, calculated based on two-way A vs. B comparison.

MEAN PLASMA DILTIAZEM CONCENTRATIONS

STUDY # 2443 (N=27)

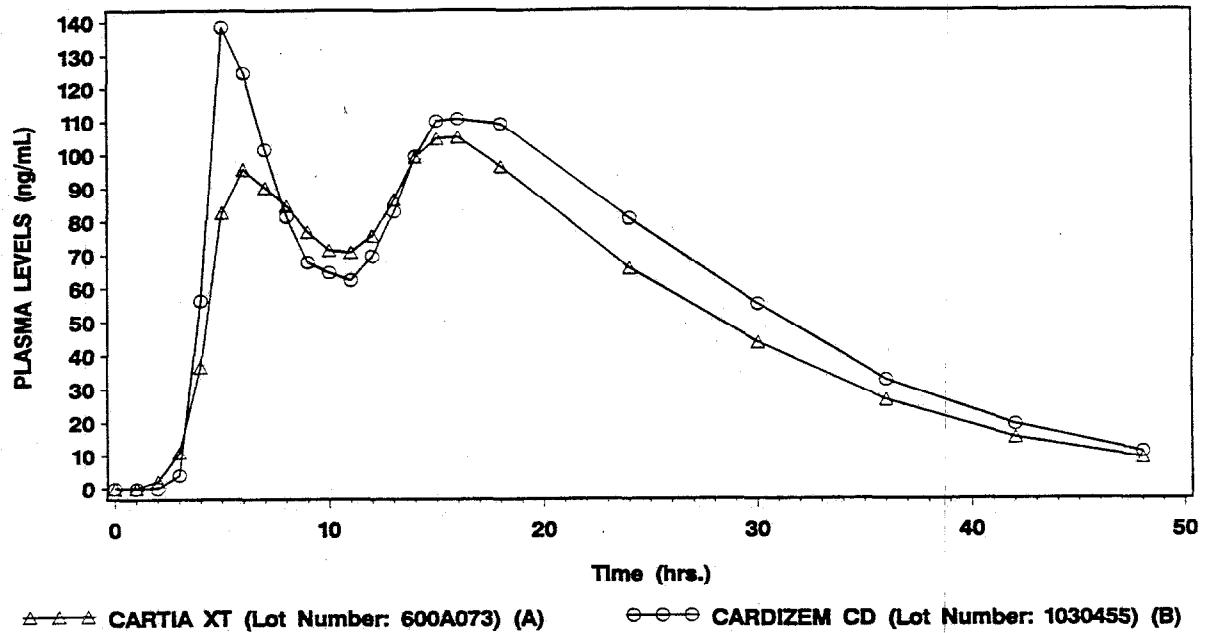


FIGURE 1.1

SEMI LOG MEAN PLASMA DILTIAZEM CONCENTRATIONS

STUDY # 2443 (N=27)

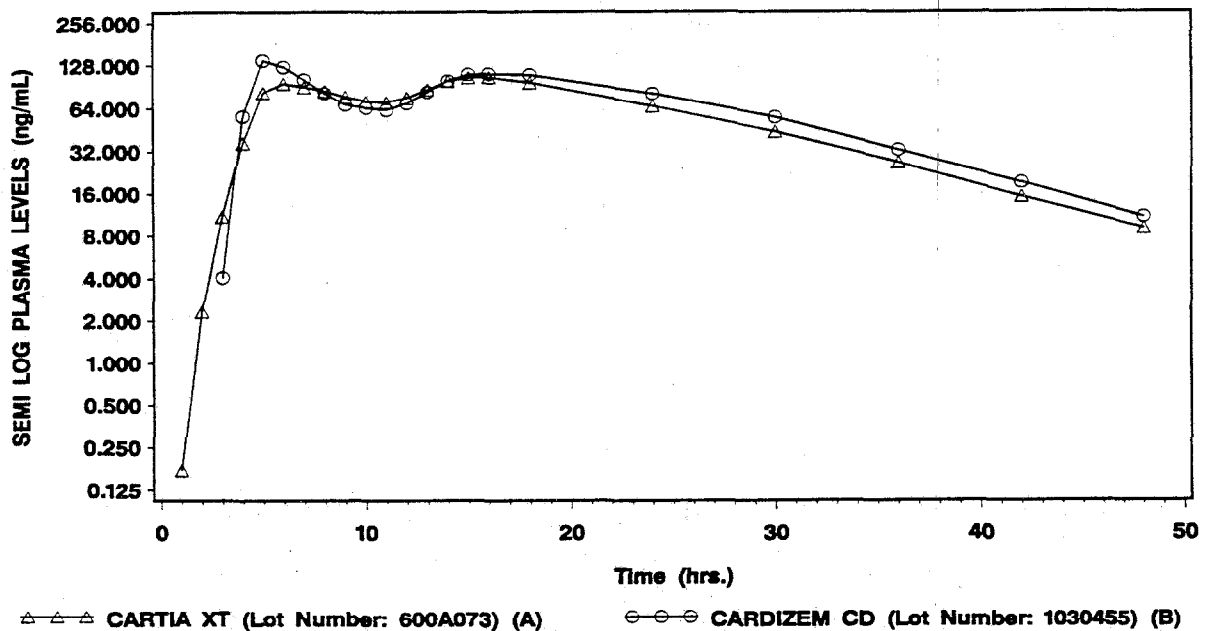


FIGURE 1.2

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 STUDY # 2443 (B01-527PK-DILG12)

SUMMARY OF RESULTS

Section 2.0: Mean Pharmacokinetic Parameters for Plasma Desacetyldiltiazem (n = 27)

Parameter	CARTIA XT TM (A) ¹	CARDIZEM [®] CD (B) ²
	Lot #: 600A073 Mean ± SD	Lot #: 1030455 Mean ± SD
AUC (0 - t) (ng · hr/mL)	300.74 ± 215.98	315.15 ± 216.80
AUC (0 - inf) (ng · hr/mL)	368.34 ± 322.78	401.18 ± 361.57
C _{max} (ng/mL)	10.48 ± 6.87	11.06 ± 7.09
T _{max} (hours)	20.07 ± 4.13	22.07 ± 4.45
t _{1/2} (hours)	12.69 ± 4.69	12.23 ± 3.68
K _{el} (hour ⁻¹)	0.060 ± 0.015	0.060 ± 0.013

CARTIA XTTM (A) vs. CARDIZEM[®] CD (B)

	AUC (0 - t)	AUC (0 - infinity)	C _{max}
90% Geometric C.I. ³	87.27 % - 101.50 %	88.58 % - 102.25 %	87.62 % - 102.48 %
Ratio of Means ⁴	94.12 %	95.17 %	94.76 %
Intra-Subject C.V. ⁵	16.24 %	15.09 %	16.84 %

¹ One (1) Cartia XTTM (diltiazem HCl extended release capsules, USP) 300 mg Capsule (Andrx Pharmaceuticals, Inc.; Lot #: 600A073; Expiry Date: 07/02) (Total dose = 300 mg).

² One (1) Cardizem[®] CD (diltiazem HCl) 300 mg Capsule (Aventis Pharmaceuticals, Inc.; Lot #: 1030455; Expiry Date: 11/2002) (Total dose = 300 mg).

³ 90% Geometric Confidence Interval using log-transformed data and CARDIZEM[®] CD (B) as the reference (Aventis Pharmaceuticals, Inc.; Lot #: 1030455; Expiry Date: 11/2002), calculated based on two-way A vs. B comparison.

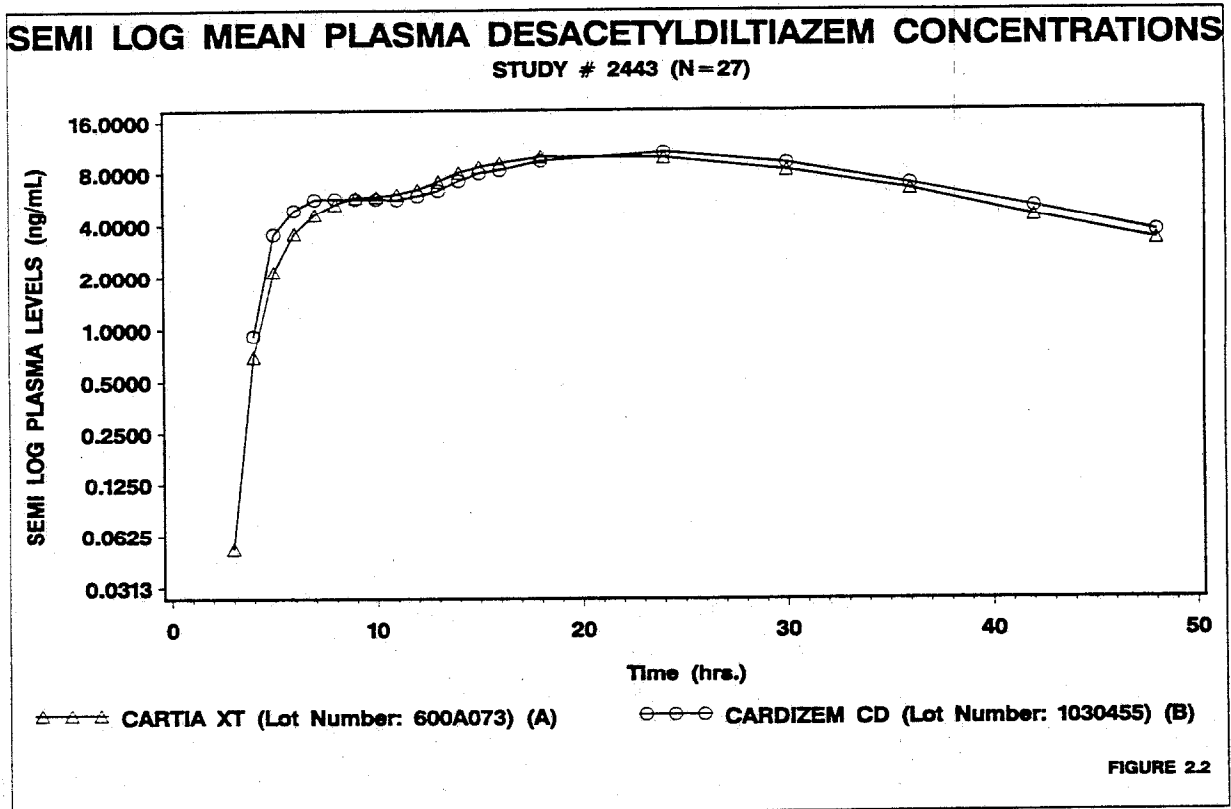
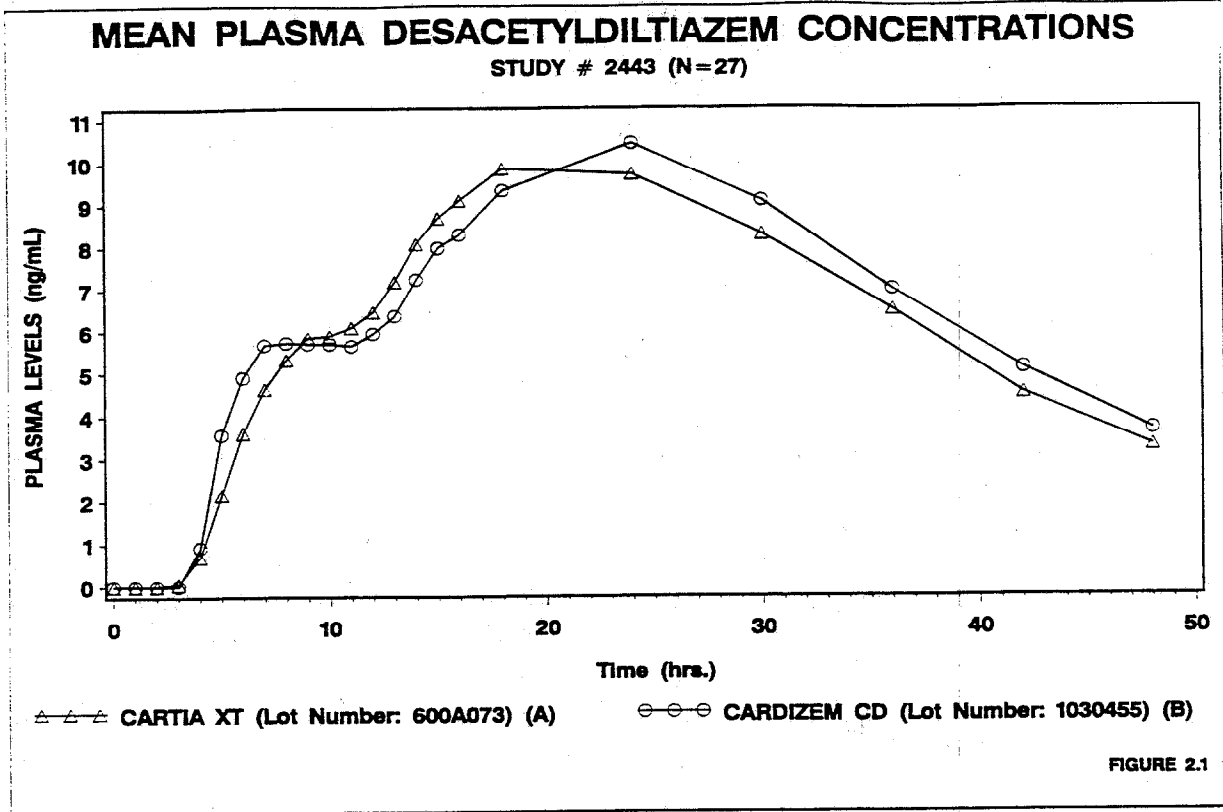
⁴ Calculated using geometric means according to the formula: $e^{(\text{CARTIA XT } \text{TM} \text{ (A)} - \text{CARDIZEM}^{\text{®}} \text{ CD (B)})} \times 100\%$, calculated based on two-way A vs. B comparison.

⁵ Intra-subject coefficient of variation for log-transformed pharmacokinetic parameter, calculated based on two-way A vs. B comparison.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 STUDY # 2443 (B01-527PK-DILG12)

Mean Plasma DESACETYLDILTIAZEM Concentrations (ng/mL)

SAMPLE TIME (HOURS)	CARTIA XT TM 1 x 300 mg			CARDIZEM [®] CD 1 x 300 mg		
	Mean Value		SD	Mean Value		SD
0.00	0.00	±	0.00	0.00	±	0.00
1.00	0.00	±	0.00	0.00	±	0.00
2.00	0.00	±	0.00	0.00	±	0.00
3.00	0.05	±	0.27	0.00	±	0.00
4.00	0.69	±	1.24	0.91	±	1.38
5.00	2.16	±	1.94	3.56	±	2.30
6.00	3.60	±	2.10	4.90	±	2.20
7.00	4.63	±	2.35	5.66	±	2.71
8.00	5.31	±	2.50	5.72	±	2.41
9.00	5.83	±	2.73	5.69	±	2.51
10.00	5.87	±	2.80	5.68	±	2.59
11.00	6.07	±	2.74	5.63	±	2.69
12.00	6.44	±	2.89	5.92	±	3.01
13.00	7.17	±	3.34	6.34	±	3.31
14.00	8.07	±	3.82	7.22	±	3.94
15.00	8.69	±	4.13	7.98	±	4.14
16.00	9.10	±	4.29	8.29	±	4.42
18.00	9.86	±	5.18	9.34	±	4.86
24.00	9.74	±	6.34	10.46	±	6.51
30.00	8.28	±	7.15	9.08	±	7.41
36.00	6.46	±	6.86	6.95	±	6.57
42.00	4.50	±	5.30	5.08	±	5.32
48.00	3.27	±	4.31	3.65	±	4.52



SUMMARY OF RESULTS

Section 3.0: Mean Pharmacokinetic Parameters for Plasma N-Desmethyldiltiazem (n = 27)

Parameter	CARTIA XT TM (A) ¹	CARDIZEM [®] CD (B) ²
	Lot #: 600A073 Mean ± SD	Lot #: 1030455 Mean ± SD
AUC (0 - t) (ng · hr/mL)	929.36 ± 285.08	1014.65 ± 325.54
AUC (0 - inf) (ng · hr/mL)	1042.92 ± 325.60	1144.95 ± 381.10
C _{max} (ng/mL)	35.22 ± 9.07	37.23 ± 11.01
T _{max} (hours)	15.04 ± 3.66	15.07 ± 5.12
t _{1/2} (hours)	10.93 ± 2.33	10.96 ± 1.84
K _{el} (hour ⁻¹)	0.066 ± 0.012	0.065 ± 0.011

CARTIA XTTM (A) vs. CARDIZEM[®] CD (B)

	AUC (0 - t)	AUC (0 - infinity)	C _{max}
90% Geometric CI. ³	87.90 % - 96.42 %	87.65 % - 96.07 %	90.25 % - 101.17 %
Ratio of Means ⁴	92.06 %	91.76 %	95.55 %
Intra-Subject C.V. ⁵	9.94 %	9.86 %	12.27 %

¹ One (1) Cartia XTTM (diltiazem HCl extended release capsules, USP) 300 mg Capsule (Andrx Pharmaceuticals, Inc.; Lot #: 600A073; Expiry Date: 07/02) (Total dose = 300 mg).

² One (1) Cardizem[®] CD (diltiazem HCl) 300 mg Capsule (Aventis Pharmaceuticals, Inc.; Lot #: 1030455; Expiry Date: 11/2002) (Total dose = 300 mg).

³ 90% Geometric Confidence Interval using log-transformed data and CARDIZEM[®] CD (B) as the reference (Aventis Pharmaceuticals, Inc.; Lot #: 1030455; Expiry Date: 11/2002), calculated based on two-way A vs. B comparison.

⁴ Calculated using geometric means according to the formula: $e^{(CARTIA\ XT\ TM\ (A) - CARDIZEM\ CD\ (B))} \times 100\%$, calculated based on two-way A vs. B comparison.

⁵ Intra-subject coefficient of variation for log-transformed pharmacokinetic parameter, calculated based on two-way A vs. B comparison.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 STUDY # 2443 (B01-527PK-DILG12)

Mean Plasma N-DESMETHYLDILTIAZEM Concentrations (ng/mL)						
SAMPLE TIME (HOURS)	CARTIA XT™ 1 x 300 mg			CARDIZEM [®] CD 1 x 300 mg		
	Mean Value		SD	Mean Value		SD
0.00	0.00	±	0.00	0.00	±	0.00
1.00	0.00	±	0.00	0.00	±	0.00
2.00	0.00	±	0.00	0.00	±	0.00
3.00	1.09	±	2.46	0.53	±	2.15
4.00	6.91	±	6.36	9.79	±	11.32
5.00	15.72	±	7.13	23.12	±	7.72
6.00	21.21	±	7.46	27.32	±	6.90
7.00	24.21	±	7.28	28.07	±	6.94
8.00	25.18	±	7.18	27.08	±	6.59
9.00	25.23	±	7.16	25.53	±	6.54
10.00	25.95	±	7.31	25.69	±	8.02
11.00	25.23	±	7.07	24.05	±	8.14
12.00	26.27	±	7.07	24.83	±	8.59
13.00	28.52	±	7.11	27.30	±	9.63
14.00	31.36	±	7.98	29.94	±	10.02
15.00	33.06	±	8.49	32.35	±	10.34
16.00	34.05	±	8.82	34.13	±	10.94
18.00	33.67	±	9.78	34.82	±	11.18
24.00	26.32	±	9.01	29.56	±	10.29
30.00	21.30	±	7.69	24.61	±	9.68
36.00	15.10	±	6.62	17.08	±	7.36
42.00	9.81	±	4.71	11.69	±	5.48
48.00	6.53	±	3.32	7.45	±	4.26

MEAN PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS STUDY # 2443 (N=27)

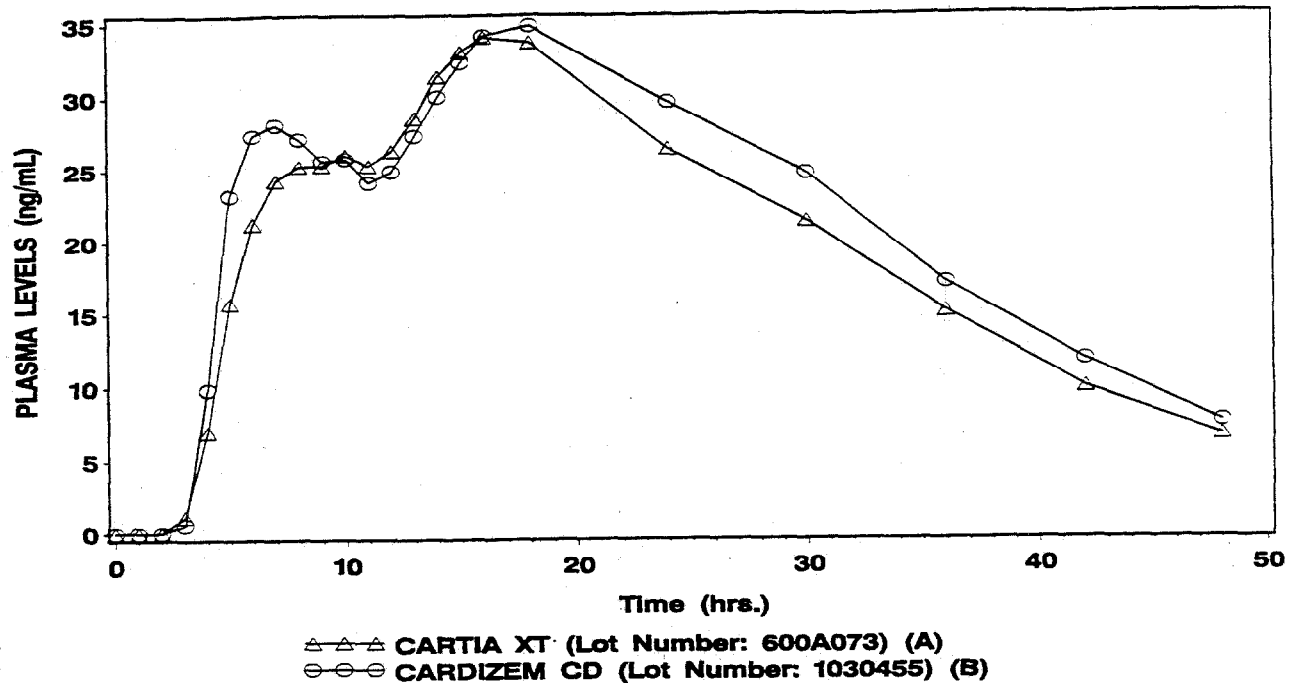


FIGURE 3.1

SEMI LOG MEAN PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS STUDY # 2443 (N=27)

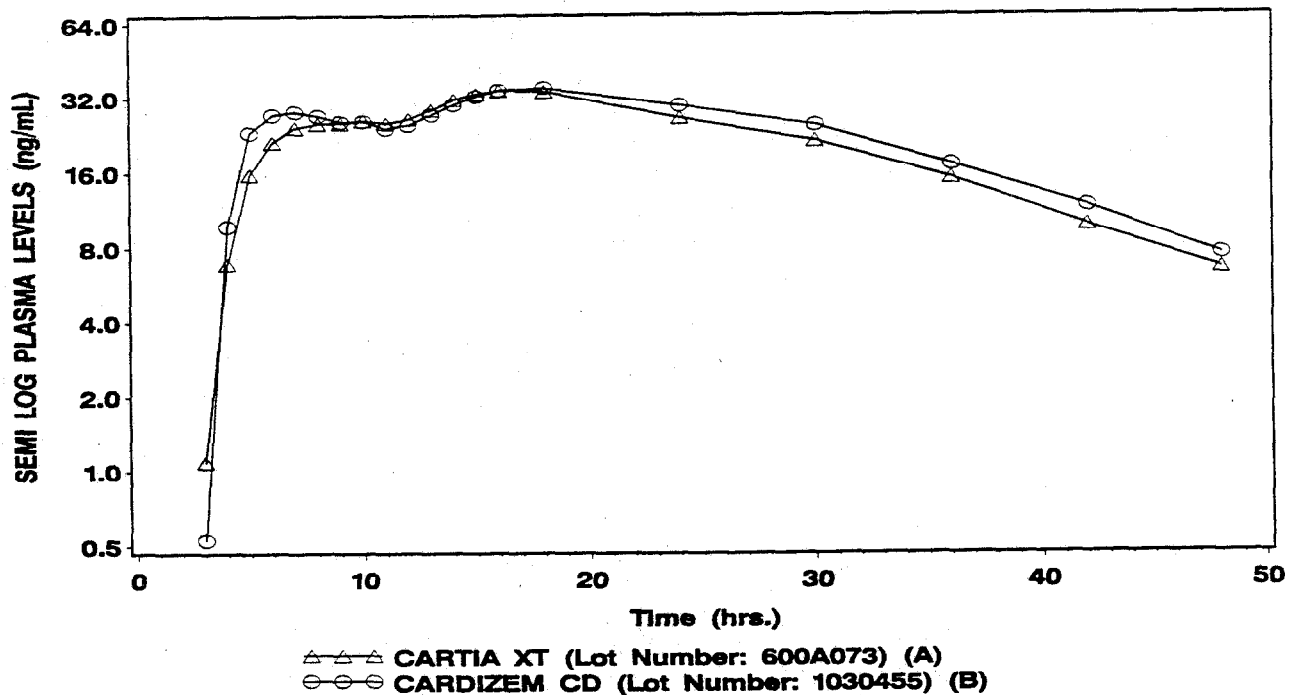


FIGURE 3.2

REPORT

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
STUDY # 2443 (B01-527PK-DILG12)

**A TWO-WAY CROSS-OVER SINGLE-DOSE OPEN-LABEL FASTING
PHARMACOKINETIC STUDY OF CARTIA XT™ 300 mg CAPSULES VERSUS
CARDIZEM® CD 300 mg CAPSULES, IN NORMAL HEALTHY NON-SMOKING
MALE SUBJECTS**

OBJECTIVE

This study was designed to evaluate the pharmacokinetics of the test product, Cartia XT™ (diltiazem HCl extended release capsules, USP) 300 mg Capsules (Andrx Pharmaceuticals, Inc.), versus the reference product, Cardizem® CD (diltiazem HCl) 300 mg Capsules (Aventis Pharmaceuticals, Inc.) under fasting conditions.

FACILITIES

The study was conducted from April 13, 2001 to April 23, 2001 at the bioavailability center of Biovail Contract Research (BCR), a division of Biovail Corporation, Toronto, Ontario, Canada. All blood chemistry, hepatitis B-surface antigen, hepatitis C, HIV, hematology and urinalysis testing were carried out by Gamma-Dynacare Medical Laboratories, Brampton, Ontario, Canada. The urine drugs of abuse and nicotine screen(s), saliva alcohol testing, analytical determination of diltiazem, desacetyldiltiazem and N-desmethyldiltiazem in the plasma samples, pharmacokinetic analyses, statistical analyses, and preparation of the final report were performed by Biovail Contract Research, a division of Biovail Corporation, Toronto, Ontario, Canada.

PROTOCOL AND INFORMED CONSENT

The study followed a randomized, open-label, single-dose, two-way, crossover design in twenty-eight (28) normal, healthy, non-smoking male subjects under fasting conditions.

The study Protocol No. 2443 (B01-527PK-DILG12) Version 1.1, and examples of the Informed Consent Form and the Informed Consent to Medical Screening form are presented in the Protocol and IRB section of this report. The Protocol and Informed Consent Form were originally reviewed and approved by the Institutional Review Board of Biovail Contract Research on March 21, 2001.

All subjects signed both the Informed Consent to Medical Screening form and the Informed Consent Form before any procedures were performed at medical screening and during the study, respectively.

STUDY DRUG INFORMATION

The Cartia XTTM (diltiazem HCl extended release capsules, USP) 300 mg Capsules (Andrx Pharmaceuticals, Inc.; Lot Number: 600A073; Expiry Date: 07/02; an oblong capsule, with "300 mg" printed in black ink on the orange cap and Andrx 600 printed in black ink on the orange body) (Treatment A) and Cardizem[®] CD (diltiazem HCl) 300 mg Capsules (Aventis Pharmaceuticals, Inc.; Lot Number: 1030455; Expiry Date: 11/2002; an oblong capsule with "cardizem CD 300 mg" printed in light grey ink on the grey body and with no markings on the blue cap) (Treatment B) were both received by the clinic facility on April 12, 2001. The details of the drug products received are outlined in the Drug Accountability Records section of this report.

The analytical facility was blinded to the randomization code. This code was broken for statistical and reporting purposes after the completion of the analytical portion.

PROCEDURES

Pre-Study Activities

All normal, healthy, non-smoking, male subjects were specifically questioned by BCR's professional staff on all restrictions outlined in the inclusion/exclusion criteria presented in sections 6.2.1 and 6.2.2 of the Protocol. Subjects were informed that concomitant medication was not permitted during the study. Subjects were requested to abstain from alcohol, grapefruit products, xanthine and caffeine containing foods and fluids for 48 hours prior to the start of each study period until the final blood draw for each period.

Subjects were a minimum of 18 years of age (inclusive), and with a body weight not more than $\pm 15\%$ of the ideal weight for the subject's height and frame, as determined by the Table of Desirable Weights for Men in the Protocol and IRB section. The demographic data for the twenty-eight (28) subjects who were dosed is presented in the Demographics Table.

Subjects had the following tests performed at Medical Screening: clinical chemistry, hematology, urinalysis, hepatitis B-surface antigen, hepatitis C, HIV screens, urine drugs of abuse, urine nicotine, saliva alcohol, ECG measurements, vital sign measurements, pre-study physical examination, and pre-study medical and medication history.

Study Activities

The subjects were institutionalized in the clinic on April 13, 2001, the evening prior to dosing and stayed until the 48.0-hour post-dosing blood draw of each study period. There was a one (1) week washout period between study periods.

Upon check-in of each study period, additional urine drugs of abuse and saliva alcohol tests were performed on all of the subjects.

Each subject received a total dose of 300 mg of diltiazem hydrochloride during each 48.0-hour study period as one (1) Cartia XT™ (diltiazem HCl extended release capsules, USP) 300 mg Capsule (Treatment A), or as one (1) Cardizem® CD (diltiazem HCl) 300 mg Capsule (Treatment B), at 0.0 hour with 240 mL of ambient temperature water. The medication was administered orally starting at 7:00 am (0.0 hour), with two (2) minute intervals between subjects, on April 14, 2001 for Period I and on April 21, 2001 for Period II. A check of each subject's mouth was made to ensure drug ingestion. Each formulation was administered according to the computer-generated randomization sequence, which is outlined in the Dosage Regimen Table. The actual time for each dosing was recorded and is tabulated in the Clinic Records (Drug Administration Records) section.

All subjects remained seated in an upright position for the first four (4) hours following drug administration and were allowed to rise under supervision only for brief periods of time to comply with study related activities or to use the washroom facilities. Throughout each study period, the subjects were monitored by BCR's professional staff for safety. The Principal Investigator, or medical designate, was on-site at least sixty (60) minutes prior to each dosing and for the first twelve (12) hours following each drug administration. The Principal Investigator, or medical designate, were also available by pager throughout the study.

Water was provided *ad libitum* until 1.0 hour pre-dose and after 1.0 hour post-drug. The only fluid intake that was allowed during this two-hour time span was 240 mL of ambient temperature water.

The subjects fasted overnight for at least ten (10) hours prior to drug administration. Meals were provided to the subjects at 4.5, 9.5, 23.5, 28.5 and 33.5 hours post-drug. In addition, a snack was provided to each subject at 13.5 and 37.5 hours post-drug. The meals and snacks, which are detailed in the Clinic Records (Menu) section, were free of xanthine, caffeine and grapefruit products and were identical between study periods.

During each study period, twenty-three (23) blood samples (7 mL each) were collected from each subject by direct venipuncture from an antecubital vein using pre-cooled, pre-labelled blood collection tubes containing potassium EDTA as the anticoagulant. Blood samples were collected at 0.0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 18.0, 24.0, 30.0, 36.0, 42.0 and 48.0 hours post-drug administration. Approximately 349 mL of blood was collected over the two study periods, including the amount for screening and post-study clinical blood tests. The clock times of all blood draws for plasma concentration analyses were recorded and are presented in the Clinic Records (Blood Sample Collection Records) section.

The blood samples were stored on ice prior to centrifugation and were centrifuged as soon as possible under refrigerated conditions at 3500 rpm for seven (7) minutes. The collected plasma from each blood collection tubes was aliquotted into labelled, duplicate, polypropylene culture and stored frozen at minus (-) 70°C ± 10°C until assayed. To ensure that the analytical facility was blinded to the randomization code, the tubes were labelled with the study number, dosing period, subject number, sampling time point, aliquot number and matrix without revealing the treatment regimen. Upon completion of the study, all

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
STUDY # 2443 (B01-527PK-DILG12)

samples were delivered to the analytical laboratory for the analysis of diltiazem, desacetyldiltiazem and N-desmethyldiltiazem in the plasma samples.

Vital signs (blood pressure and heart rate) were monitored at the following time points relative to drug administration during each study period: 0.0 (pre-dose), 2.0, 4.0, 8.0 and 12.0 hours post-dose. Vital signs were repeated as required by the protocol.

The 12-lead ECG monitoring was also carried out at the following time points relative to drug administration: 0.0 (pre-dose), 2.0, 4.0, 8.0 and 12.0 hours post-dose. All subjects that were dosed had a PR/PQ interval of equal to or less than 210 msec. ECG results that were outside of the specified range were reviewed by the Principal Investigator (or designate). Following this review, subjects were only allowed to continue the study based on the discretion of the Principal Investigator (or designate).

Subject #02 withdrew during the washout period of Period I due to personal reasons. Following post-study physical examination, vital sign measurements and laboratory tests, as outlined in the Protocol, twenty-seven (27) subjects were able to complete the study under the direction of P. Y. Tam, M.D., F.R.C.P., F.A.C.P. (Principal Investigator), Dr. G. R. Nagai, M.D. (Medical Associate), Dr. E. Pavone, M.D. (Medical Associate), Dr. S. Fung, M.D. (Medical Associate), Dr. G. Logsetty, M.D. and Dr. B. Lau, M.D. (Medical Associate). The analytical determination, pharmacokinetic analyses and statistical analyses of plasma diltiazem, desacetyldiltiazem and N-desmethyldiltiazem data were conducted on twenty-seven (27) evaluable subjects that completed the study.

ADVERSE EVENTS

During this study, eleven (11) subjects experienced a total of nineteen (19) adverse events.

During Period I, seven (7) subjects experienced a total of ten (10) adverse events. These adverse events consisted of four (4) episodes of headache, two (2) episodes of nausea and one (1) episode each of loose stool, dizziness and vomiting. During the washout of Period I Subject #02 experienced one (1) episode of decreased glucose. The adverse events were all mild in severity at onset, with the exception of one (1) moderate episode of dizziness. All adverse events were resolved spontaneously. All of these subjects were able to complete the study period.

During Period II, six (6) subjects experienced a total of nine (9) adverse events. These adverse events consisted of one (1) episode each of headache, elevated protein in urine, decreased neutrophil count, decreased WBC count, decreased calcium, leukocytes in urine, elevated glucose, elevated ALT and dizziness. The adverse events were all mild in severity at onset. All adverse events were resolved spontaneously. All of these subjects were able to complete the study period.

The Adverse Event Records are presented in the Clinic Records section and are summarized in the Adverse Events table.

Other study details are located in the protocol (Protocol and IRB section).

PROTOCOL DEVIATIONS

There were no protocol deviations reported in this study and twenty-seven (27) blood sampling time deviations were reported in this study.

A total of sixteen (16) blood sampling time deviations were reported during Period I. The blood sampling time deviations occurred from 2.0 hours to 48.0 hours post-drug and ranged from one (1) minute to four (4) minutes in length. One (1) deviation resulted from an inconclusive sampling time.

A total of eleven (11) blood sampling time deviations were reported during Period II. The blood sampling time deviations occurred from 1.0 hour to 48.0 hours post-drug and ranged from one (1) minute to two (2) minutes in length.

The above mentioned sampling time deviations did not impact on the calculation of pharmacokinetic parameters, since all calculations were carried out using actual sampling time-points.

The Protocol Deviations record for each period is presented in the Clinic Records section and is summarized in the Protocol Deviations table and the Blood Sampling Time Deviations table.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 STUDY # 2443 (B01-527PK-DILG12)

**CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg
 CAPSULES
 STUDY # 2443 (B01-527PK-DILG12)
 DEMOGRAPHICS**

SUBJECT NO.	RACE	GENDER	AGE (years)	HEIGHT (inches)	WEIGHT (pounds)	SMOKER	FRAME	SERUM CREATININE ($\mu\text{mol/L}$)
01	Caucasian	Male	36	67	169	No	Medium	78
02	Black	Male	33	68	172	No	Large	82
03	Black	Male	23	70	200	No	Large	79
04	Asian	Male	34	73	202	No	Large	98
05	Caucasian	Male	43	73	182	No	Medium	89
06	Black	Male	24	70	192	No	Large	99
07	Caucasian	Male	24	71	200	No	Large	99
08	Caucasian	Male	33	76	188	No	Medium	82
09	Caucasian	Male	36	70	153	No	Medium	112
10	Caucasian	Male	24	76	238	No	Large	81
11	Black	Male	35	67	189	No	Large	102
12	Caucasian	Male	24	74	187	No	Medium	87
13	Caucasian	Male	38	71	199	No	Large	116
14	Caucasian	Male	42	73	182	No	Medium	88
15	Caucasian	Male	36	68	167	No	Medium	98
16	Caucasian	Male	35	65	169	No	Medium	93
17	Caucasian	Male	29	70	170	No	Medium	82
18	Caucasian	Male	29	71	164	No	Medium	89
19	Asian	Male	44	66	157	No	Medium	87
20	Black	Male	30	71	178	No	Medium	100
21	Caucasian	Male	20	69	182	No	Medium	94
22	Caucasian	Male	34	74	166	No	Medium	97
23	Asian	Male	24	73	164	No	Medium	92
24	Caucasian	Male	34	71	182	No	Medium	110
25	Caucasian	Male	44	70	166	No	Medium	101
26	Caucasian	Male	28	73	175	No	Medium	83
27	Hispanic	Male	19	70	130	No	Medium	89
28	Caucasian	Male	39	66	154	No	Medium	86
			MEAN	32	71	185		
			S.D.(\pm)	6.3	3.1	19.6		

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 STUDY # 2443 (B01-527PK-DILG12)

**CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg
 CAPSULES
 STUDY # 2443 (B01-527PK-DILG12)
 DOSAGE REGIMEN**

SUBJECT NUMBER	PERIOD I 04-14-2001	PERIOD II 04-21-2001
01	A	B
*02	A	B
03	A	B
04	B	A
05	B	A
06	B	A
07	B	A
08	A	B
09	B	A
10	A	B
11	A	B
12	A	B
13	B	A
14	A	B
15	A	B
16	B	A
17	A	B
18	A	B
19	B	A
20	A	B
21	A	B
22	A	B
23	B	A
24	B	A
25	B	A
26	B	A
27	B	A
28	B	A

*Subject #02 withdrew during the washout period of Period I due to personal reasons.

- A) Cartia XT™ (diltiazem HCl extended release capsules, USP) 300 mg Capsules (Andrx Pharmaceuticals, Inc.) Lot #: 600A073 ; Expiry Date: 07/02**

One (1) Cartia XT™ (diltiazem HCl extended release capsules, USP) 300 mg Capsule with 240 mL of ambient temperature water, following an overnight fast of at least ten (10) hours
 (Total dose = 300 mg).

- B) Cardizem® CD (diltiazem HCl) 300 mg Capsules (Aventis Pharmaceuticals, Inc.) Lot #: 1030455; Expiry Date: 11/2002**

One (1) Cardizem® CD (diltiazem HCl) 300 mg Capsule with 240 mL of ambient temperature water, following an overnight fast of at least ten (10) hours (Total dose = 300 mg).

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
STUDY # 2443 (B01-527PK-DILG12)

**CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg
CAPSULES
STUDY # 2443 (B01-527PK-DILG12)
BLOOD SAMPLING TIME DEVIATIONS**

PERIOD	SUBJECT NUMBER	SCHEDULED TIMEPOINT	STD (minutes)
I	02	42.0	+1
I	03	2.0	+2
I	03	14.0	+1
I	03	24.0	+1
I	04	13.0	+1
I	04	15.0	+2
I	04	16.0	+4
I	04	42.0	+1
I	04	48.0	+1
I	06	2.0	INCONCLUSIVE
I	18	48.0	+1
I	22	3.0	+4
I	22	18.0	+1
I	23	5.0	+1
I	27	12.0	+1
I	27	16.0	+2

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
STUDY # 2443 (B01-527PK-DILG12)

**CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg
CAPSULES**

STUDY # 2443 (B01-527PK-DILG12)

BLOOD SAMPLING TIME DEVIATIONS (Cont'd)

PERIOD	SUBJECT NUMBER	SCHEDULED TIMEPOINT	STD (minutes)
II	01	48.0	+1
II	04	1.0	+2
II	04	12.0	+1
II	04	16.0	+2
II	04	36.0	+1
II	04	48.0	+1
II	15	30.0	+1
II	16	11.0	+1
II	17	30.0	+1
II	28	13.0	+1
II	28	16.0	+1

CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg CAPSULES
STUDY # 2443 (B01-527PK-DILG12)
SUMMARY OF ADVERSE EVENTS

SUBJECT NUMBER	PERIOD	REGIMEN*	SYMPTOMS	OCURRENCE (Pre-dose / Post-dose)	DATE OF ONSET (mm-dd-yyyy)	TIME OF ONSET (24 hour clock)	SEVERITY** AT ONSET	TIME OF RESOLUTION (24 hour clock)	DATE OF RESOLUTION (mm-dd-yyyy)	DURATION (hh: mm)	RESOLUTION (Spontaneous/ With Treatment/ Unresolved)	ACTIONS TAKEN	RELATIONSHIP TO STUDY DRUG***
02	I	A	Decreased glucose	Post-dose	04-25-2001	09:37	Mild	19:11	04-28-2001	81:34	Spontaneous	Subject was called and appointment made – repeat done	Unrelated
04	I	B	Headache	Post-dose	04-14-2001	17:00	Mild	08:30	04-15-2001	15:30	Spontaneous	Ice pack offered, subject refused	Probably
05	I	B	Nausea	Post-dose	04-15-2001	15:30	Mild	18:00	04-15-2001	2:30	Spontaneous	Encouraged subject to drink fluids if able to tolerate	Unlikely
			Loose stool	Post-dose	04-15-2001	15:30	Mild	06:50	04-16-2001	15:20	Spontaneous	Encouraged subject to drink fluids if able to tolerate and subject asked if he wants to be seen by a doctor and he refused. Naked eye examination done	Unrelated
11	I	A	Headache	Post-dose	04-14-2001	12:00	Mild	06:15	04-15-2001	18:15	Spontaneous	Ice pack given to the subject	Probably
22	I	A	Dizziness	Post-dose	04-14-2001	10:48	Moderate	11:00	04-14-2001	0:12	Spontaneous	Assisted subject to wheelchair, vitals taken	Probably
23	I	B	Nausea	Post-dose	04-14-2001	17:00	Mild	18:30	04-14-2001	1:30	Spontaneous	None	Unlikely
			Headache	Post-dose	04-14-2001	17:00	Mild	23:35	04-14-2001	6:35	Spontaneous	None	Probably
			Vomiting	Post-dose	04-14-2001	17:35	Mild	17:40	04-14-2001	0:05	Spontaneous	Advised to take oral fluids (water)	Unlikely
26	I	B	Headache	Post-dose	04-14-2001	15:10	Mild	23:28	04-14-2001	8:18	Spontaneous	None	Probably

CODES:

***REGIMEN**

- A: One (1) Cartia XT™ (diltiazem HCl extended release capsules, USP) 300 mg Capsule (Andrx Pharmaceuticals, Inc.; Lot #: 600A073 ; Expiry Date: 07/02) with 240 mL of ambient temperature water, following an overnight fast of at least ten (10) hours (Total dose = 300 mg).
- B: One (1) Cardizem® CD (diltiazem HCl) 300 mg Capsule (Aventis Pharmaceuticals, Inc.; Lot #: 1030455; Expiry Date: 11/2002) with 240 mL of ambient temperature water, following an overnight fast of at least ten (10) hours (Total dose = 300 mg).

****SEVERITY**

- MILD: Awareness of symptom but does not interfere with routine activities.
MODERATE: Discomfort enough to interfere with routine activities.
SEVERE: Impossible to perform routine activities.

*****RELATIONSHIP TO STUDY DRUG**

- CERTAIN: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drug or chemicals. The response to withdrawal of the drug (re-challenge) should be clinically plausible. Re-challenge information is required to fulfill this criterion.
- PROBABLY: A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (re-challenge). Re-challenge information is not required to fulfill this criterion.
- POSSIBLY: A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- UNLIKELY: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and which other drugs, chemicals or underlying disease provide plausible explanation.
- UNRELATED: This category is applicable to the Adverse Events which are judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.) and do not meet the criteria for drug relationship listed under the above mentioned conditions.

**CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg CAPSULES
STUDY # 2443 (B01-527PK-DILG12)**

SUMMARY OF ADVERSE EVENTS (Cont'd)

SUBJECT NUMBER	PERIOD	REGIMEN*	SYMPTOMS	OCURRENCE (Pre-dose / Post-dose)	DATE OF ONSET (mm-dd-yyyy)	TIME OF ONSET (24 hour clock)	SEVERITY** AT ONSET	TIME OF RESOLUTION (24 hour clock)	DATE OF RESOLUTION (mm-dd-yyyy)	DURATION (hh: mm)	RESOLUTION (Spontaneous/ With Treatment/ Unresolved)	ACTIONS TAKEN	RELATIONSHIP TO STUDY DRUG***
11	II	B	Headache	Post-dose	04-21-2001	11:00	Mild	06:00	04-22-2001	19:00	Spontaneous	None	Probably
			Elevated protein in urine	Post-dose	04-24-2001	01:59	Mild	Unknown	04-27-2001	Unknown	Spontaneous	None - Repeat done	Unrelated
14	II	B	Decreased neutrophil count	Post-dose	04-24-2001	01:59	Mild	23:49	05-14-2001	501:50	Spontaneous	Tried to contact subject (x3), sent registered letter - Repeat done	Unrelated
			Decreased WBC count	Post-dose	04-24-2001	01:59	Mild	23:49	05-14-2001	501:50	Spontaneous	Tried to contact subject (x3), sent registered letter - Repeat done	Unrelated
			Decreased calcium	Post-dose	04-24-2001	01:59	Mild	23:49	05-14-2001	501:50	Spontaneous	Tried to contact subject (x3), sent registered letter - Repeat done	Unrelated
20	II	B	Leukocytes in urine	Post-dose	04-24-2001	01:59	Mild	Unknown	04-27-2001	Unknown	Spontaneous	Subject called and appointment made - Repeat done	Unrelated
22	II	B	Elevated glucose	Post-dose	04-24-2001	01:59	Mild	19:30	04-30-2001	161:31	Spontaneous	Message was given to subject for repeat test - Repeat done	Unrelated
24	II	A	Elevated ALT	Post-dose	04-24-2001	01:59	Mild	18:04	04-29-2001	136:05	Spontaneous	Subject called (x2) and appointment made	Unrelated
27	II	A	Dizzy	Post-dose	04-21-2001	09:40	Mild	09:45	04-21-2001	0:05	Spontaneous	None	Unlikely

CODES:

***REGIMEN**

- A: One (1) Cartia XT™ (diltiazem HCl extended release capsules, USP) 300 mg Capsule (Andrx Pharmaceuticals, Inc.; Lot #: 600A073 ; Expiry Date: 07/02) with 240 mL of ambient temperature water, following an overnight fast of at least ten (10) hours (Total dose = 300 mg).
- B: One (1) Cardizem® CD (diltiazem HCl) 300 mg Capsule (Aventis Pharmaceuticals, Inc.; Lot #: 1030455; Expiry Date: 11/2002) with 240 mL of ambient temperature water, following an overnight fast of at least ten (10) hours (Total dose = 300 mg).

****SEVERITY**

- MILD: Awareness of symptom but does not interfere with routine activities.
MODERATE: Discomfort enough to interfere with routine activities.
SEVERE: Impossible to perform routine activities.

*****RELATIONSHIP TO STUDY DRUG**

- CERTAIN: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drug or chemicals. The response to withdrawal of the drug (re-challenge) should be clinically plausible. Re-challenge information is required to fulfill this criterion.
- PROBABLY: A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (re-challenge). Re-challenge information is not required to fulfill this criterion.
- POSSIBLY: A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- UNLIKELY: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and which other drugs, chemicals or underlying disease provide plausible explanation.
- UNRELATED: This category is applicable to the Adverse Events which are judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.) and do not meet the criteria for drug relationship listed under the above mentioned conditions.

PHARMACOKINETIC AND STATISTICAL ANALYSES

The plasma concentration data for diltiazem, desacetyldiltiazem and N-desmethyldiltiazem were transferred by diskette from the analytical facility to the Pharmacokinetics and Statistics department at Biovail Contract Research, a division of Biovail Corporation. A minimum of 5% of the numbers were verified against a hard copy of the data.

The arithmetic mean, standard deviation (SD) and inter-subject coefficient of variation (CV) were calculated for plasma diltiazem, desacetyldiltiazem and N-desmethyldiltiazem concentrations for each sampling time and regimen. As well, the arithmetic mean, SD and inter-subject CV were calculated for the AUC (0 - t hours) (ng·hr/mL), AUC (0 - infinity) (ng·hr/mL), C_{max} (ng/mL), T_{max} (hours), $t_{1/2}$ (hours), K_{el} (hour⁻¹) and r-value (the correlation coefficient of the most linear portion of the terminal elimination phase).

The calculation of these pharmacokinetic parameters is explained below.

1. Areas Under the Plasma Concentration-Time Curves

The AUC (0 - t hours) was derived where t is the time (t) of the last measurable (non-zero) plasma concentration (C_t) for each regimen. The AUC (0 - infinity) was calculated as:

$$(AUC_{0 - infinity}) = (AUC_{0 - t}) + \frac{C_t}{K_{el}}$$

where: C_t = the last non-zero plasma concentration for that regimen, and
 (AUC_{0-t}) = the AUC from zero time to the time of the last non-zero plasma concentration for that regimen; K_{el} calculations are explained overleaf.

2. Peak Plasma Concentrations and Time to Reach Peak Concentrations

The peak plasma concentration reached (C_{\max}) and the time to reach peak concentration (T_{\max}) were also determined for each subject and regimen.

3. Plasma Half-Life and Elimination Rate Constant

To calculate the elimination rate constant (K_{el}), regression analyses were performed on the natural log (Ln) of plasma concentration values (ng/mL, y-axis) versus time (hours, x-axis). Calculations were based on the most linear portion of the terminal elimination phase as shown in semi-log plots of individual subject data. An arrow in the plot indicates the point at which each calculation began. The K_{el} was taken as the slope multiplied by (-1) and the apparent half-life ($t_{1/2}$) as $\text{Ln}2/K_{el}$.

Individual analyses of variance (ANOVAs with factors including treatment, period, sequence, and subject within sequence) were carried out on the untransformed data to compare the T_{\max} , $t_{1/2}$ and K_{el} between regimens. ANOVAs were also performed on the log-transformed data for AUC (0 - t hours), AUC (0 - infinity) and C_{\max} . The transformations were based on a natural logarithmic scale. All ANOVAs were performed with the SAS General Linear Models Procedure (GLM). For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.050.

Based on the pair-wise comparisons of the log-transformed AUC (0 - t hours), AUC (0 - infinity) and C_{\max} data, the intra-subject coefficient of variation, the relative ratios of the geometric means (calculated according to the formula: $e^{[Test-Reference]} \times 100\%$), and the 90% geometric confidence intervals were determined. In addition, the frequency distributions of the regimen differences and ratios among subjects were plotted.

EXPERIMENTAL RESULTS

Section 1.0: Plasma Diltiazem Data

This section presents the results of the pharmacokinetic and statistical analyses on the plasma diltiazem data of twenty-seven (27) evaluable subjects (n = 27).

Plasma Diltiazem Concentrations

The plasma diltiazem concentrations for each subject and sampling times are outlined in Table 1.1 for Regimen A (Andrx Pharmaceuticals, Inc. – Cartia XT™ (diltiazem HCl extended release capsules, USP) 300 mg Capsule formulation taken under fasting conditions) and in Table 1.2 for Regimen B (Aventis Pharmaceuticals, Inc. – Cardizem® CD (diltiazem HCl) 300 mg Capsule formulation taken under fasting conditions). The plots of the mean plasma diltiazem levels for the two (2) regimens over the 48.0 hour sampling period are presented in Figures 1.1 through 1.2 in linear and semi-log formats. The individual subject data, also presented in linear and semi-log formats, is displayed in Figures 1.3 through 1.83.

Figures 1.84 through 1.87 present the plots of the plasma diltiazem concentrations in linear format for all subjects in the test and reference groups.

Pharmacokinetic Parameters for Each Subject

Tables 1.3 and 1.4 report the diltiazem pharmacokinetic parameters for each subject according to regimen.

Area Under the Plasma Diltiazem Concentration-Time Curve (0 - t hours)

The area under the plasma diltiazem concentration-time curve (0 - t hours) was calculated for each subject and regimen (Table 1.5). The arithmetic means (\pm SD) are presented below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
AUC(0-t hours) (ng-hr/mL)	2459.96 \pm 1086.85	2818.93 \pm 1350.22

The ANOVA was performed on the log-transformed AUC (0 - t hours) data (Table 1.6). The 90% geometric confidence interval, ratio of means, and intra-subject coefficient of variation were also determined, based on pair-wise comparisons of the AUC (0 - t hours) data. The results are presented in Table 1.7 and are reported below:

AUC (0 - t hours)	90% Geometric C.I.	Ratio of Means	Intra-Subject C.V.
CARTIA XT™ (A) vs. CARDIZEM® CD (B)	82.23 % - 95.01 %	88.39 %	15.52 %

The frequency distribution of the regimen differences and ratios of the AUC (0 - t hours) values among subjects are presented in Figures 1.A to 1.B.

Area Under the Plasma Diltiazem Concentration-Time Curve (0 - infinity)

The AUC (0 - infinity) data for each subject and regimen was evaluated and is presented in Table 1.8. The arithmetic mean (\pm SD) for each regimen is presented overleaf:

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 STUDY # 2443 (B01-527PK-DILG12)

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
AUC(0 - infinity) (ng·hr/mL)	2583.31 ± 1151.26	2949.87 ± 1434.92

The ANOVA was performed on the log-transformed AUC (0 - infinity) data (Table 1.9). The 90% geometric confidence interval, ratio of means, and intra-subject coefficient of variation were also determined, based on the pair-wise comparisons of the AUC (0 - infinity) data. The results are presented in Table 1.10 and are reported below:

AUC (0 - infinity)	90% Geometric C.I.	Ratio of Means	Intra-Subject C.V.
CARTIA XT™ vs. CARDIZEM® CD	82.89 % - 95.36 %	88.90 %	15.06 %

The frequency distribution of the regimen differences and ratios of the AUC (0 - infinity) values among subjects are presented in Figures 1.C to 1.D.

Peak Plasma Diltiazem Concentrations

The peak, or maximal, plasma diltiazem concentrations were determined for each subject and regimen (Table 1.11). The arithmetic means (\pm SD) were calculated and are presented below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
C_{max} (ng/mL)	121.29 ± 51.30	152.32 ± 70.88

The ANOVA was performed on the log-transformed C_{max} data (Table 1.12). The 90% geometric confidence interval, ratio of means, and intra-subject coefficient of variation were also determined, based on the pair-wise comparisons of the C_{max} data. The results are reported in Table 1.13 and are presented overleaf:

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 STUDY # 2443 (B01-527PK-DILG12)

C_{max}	90% Geometric C.I.	Ratio of Means	Intra-Subject C.V.
CARTIA XTTM (A) vs. CARDIZEM[®] CD (B)	73.84 % - 89.37 %	81.23 %	20.52 %

The frequency distribution of the regimen differences and ratios of the C_{max} values among subjects are presented in Figures 1.E to 1.F.

Time to Reach Peak Plasma Diltiazem Concentrations

The time to reach peak plasma diltiazem concentrations was determined for each subject and regimen (Table 1.14). The arithmetic means (\pm SD) are presented below:

	CARTIA XTTM (A) 1 x 300 mg	CARDIZEM[®] CD (B) 1 x 300 mg
T_{max} (hours)	11.22 \pm 4.70	7.22 \pm 4.41

The ANOVA was performed on the T_{max} (Table 1.15).

The Apparent Half-Life and Elimination Rate Constant of Plasma Diltiazem

Table 1.16 presents the apparent half-life of plasma diltiazem for each subject and regimen. The arithmetic means (\pm SD) were calculated and are presented below:

	CARTIA XTTM (A) 1 x 300 mg	CARDIZEM[®] CD (B) 1 x 300 mg
$t_{1/2}$ (hours)	8.11 \pm 1.90	7.59 \pm 1.24

Table 1.17 reports the results of the ANOVA performed on the $t_{1/2}$ data.

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
STUDY # 2443 (B01-527PK-DILG12)

The elimination rate constant of plasma diltiazem was calculated for each subject and regimen, and the results are presented in Table 1.18. The arithmetic means (\pm SD) are reported below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
K_{el} (hour ⁻¹)	0.089 \pm 0.017	0.094 \pm 0.015

The ANOVA was performed on the K_{el} data (Table 1.19). The correlation coefficient (r value) of the most linear portion of the terminal elimination phase was also determined for each subject and regimen (Table 1.20).

EXPERIMENTAL RESULTS

Section 2.0: Plasma Desacetyldiltiazem Data

This section presents the results of the pharmacokinetic and statistical analyses on the plasma desacetyldiltiazem data of twenty-seven (27) evaluable subjects ($n = 27$).

Plasma Desacetyldiltiazem Concentrations

The plasma desacetyldiltiazem concentrations for each subject and sampling times are outlined in Table 2.1 for Regimen A (Andrx Pharmaceuticals, Inc. – Cartia XTTM (diltiazem HCl extended release capsules, USP) 300 mg Capsule formulation taken under fasting conditions) and in Table 2.2 for Regimen B (Aventis Pharmaceuticals, Inc. – Cardizem[®] CD (diltiazem HCl) 300 mg Capsule formulation taken under fasting conditions). The plots of the mean plasma desacetyldiltiazem levels for the two (2) regimens over the 48.0 hour sampling period are presented in Figures 2.1 through 2.2 in linear and semi-log formats. The individual subject data, also presented in linear and semi-log formats, is displayed in Figures 2.3 through 2.83.

Figures 2.84 through 2.87 present the plots of the plasma diltiazem concentrations in linear format for all subjects in the test and reference groups.

Pharmacokinetic Parameters for Each Subject

Tables 2.3 and 2.4 report the desacetyldiltiazem pharmacokinetic parameters for each subject according to regimen.

Area Under the Plasma Desacetyldiltiazem Concentration-Time Curve (0 - t hours)

The area under the plasma desacetyldiltiazem concentration-time curve (0 - t hours) was calculated for each subject and regimen (Table 2.5). The arithmetic means (\pm SD) are presented below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
AUC (0-t hours) (ng-hr/mL)	300.74 \pm 215.98	315.15 \pm 216.80

The ANOVA was performed on the log-transformed AUC (0 - t hours) data (Table 2.6). The 90% geometric confidence interval, ratio of means, and intra-subject coefficient of variation were also determined, based on pair-wise comparisons of the AUC (0 - t hours) data. The results are presented in Table 2.7 and are reported below:

AUC (0 - t hours)	90% Geometric C.I.	Ratio of Means	Intra-Subject C.V.
CARTIA XT™ (A) vs. CARDIZEM® CD (B)	87.27 % - 101.50 %	94.12 %	16.24 %

The frequency distribution of the regimen differences and ratios of the AUC (0 - t hours) values among subjects are presented in Figures 2.A to 2.B.

Area Under the Plasma-Desacetyldiltiazem Concentration-Time Curve (0 - infinity)

The AUC (0 - infinity) data for each subject and regimen was evaluated and is presented in Table 2.8. The arithmetic mean (\pm SD) for each regimen is presented overleaf:

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 STUDY # 2443 (B01-527PK-DILG12)

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
AUC (0 - infinity) (ng·hr/mL)	368.34 ± 322.78	401.18 ± 361.57

The ANOVA was performed on the log-transformed AUC (0 - infinity) data (Table 2.9). The 90% geometric confidence interval, ratio of means, and intra-subject coefficient of variation were also determined, based on the pair-wise comparisons of the AUC (0 - infinity) data. The results are presented in Table 2.10 and are reported below:

AUC (0 - infinity)	90% Geometric C.I.	Ratio of Means	Intra-Subject C.V.
CARTIA XT™ (A) vs. CARDIZEM® CD (B)	88.58 % - 102.25 %	95.17 %	15.09 %

The frequency distribution of the regimen differences and ratios of the AUC (0 - infinity) values among subjects are presented in Figures 2.C to 2.D.

Peak Plasma Desacetyldiltiazem Concentrations

The peak, or maximal, plasma desacetyldiltiazem concentrations were determined for each subject and regimen (Table 2.11). The arithmetic means (\pm SD) were calculated and are presented below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
C_{max} (ng/mL)	10.48 ± 6.87	11.06 ± 7.09

The ANOVA was performed on the log-transformed C_{max} data (Table 2.12). The 90% geometric confidence interval, ratio of means, and intra-subject coefficient of variation were also determined, based on the pair-wise comparisons of the C_{max} data. The results are reported in Table 2.13 and are presented overleaf:

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 STUDY # 2443 (B01-527PK-DILG12)

C_{max}	90% Geometric C.I.	Ratio of Means	Intra-Subject C.V.
CARTIA XT™ (A) vs. CARDIZEM® CD (B)	87.62 % - 102.48 %	94.76 %	16.84 %

The frequency distribution of the regimen differences and ratios of the C_{max} values among subjects are presented in Figures 2.E to 2.F.

Time to Reach Peak Plasma Desacetyldiltiazem Concentrations

The time to reach peak plasma desacetyldiltiazem concentrations was determined for each subject and regimen (Table 2.14). The arithmetic means (\pm SD) are presented below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
T_{max} (hours)	20.07 \pm 4.13	22.07 \pm 4.45

The ANOVA was performed on the T_{max} (Table 2.15).

The Apparent Half-Life and Elimination Rate Constant of Plasma Desacetyldiltiazem

Table 2.16 presents the apparent half-life of plasma desacetyldiltiazem for each subject and regimen. The arithmetic means (\pm SD) were calculated and are presented below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
$t_{1/2}$ (hours)	12.69 \pm 4.69	12.23 \pm 3.68

Table 2.17 reports the results of the ANOVA performed on the $t_{1/2}$ data.

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
STUDY # 2443 (B01-527PK-DILG12)

The elimination rate constant of plasma desacetyldiltiazem was calculated for each subject and regimen, and the results are presented in Table 2.18. The arithmetic means (\pm SD) are reported below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
K_{e1} (hour ⁻¹)	0.060 \pm 0.015	0.060 \pm 0.013

The ANOVA was performed on the K_{e1} data (Table 2.19). The correlation coefficient (r value) of the most linear portion of the terminal elimination phase was also determined for each subject and regimen (Table 2.20).

EXPERIMENTAL RESULTS

Section 3.0: Plasma N-Desmethyldiltiazem Data

This section presents the results of the pharmacokinetic and statistical analyses on the plasma N-desmethyldiltiazem data of twenty-seven (27) evaluable subjects (n = 27).

Plasma N-Desmethyldiltiazem Concentrations

The plasma N-desmethyldiltiazem concentrations for each subject and sampling times are outlined in Table 3.1 for Regimen A (Andrx Pharmaceuticals, Inc. – Cartia XT™ (diltiazem HCl extended release capsules, USP) 300 mg Capsule formulation taken under fasting conditions) and in Table 3.2 for Regimen B (Aventis Pharmaceuticals, Inc. – Cardizem® CD (diltiazem HCl) 300 mg Capsule formulation taken under fasting conditions). The plots of the mean plasma N-desmethyldiltiazem levels for the two (2) regimens over the 48.0 hour sampling period are presented in Figures 3.1 through 3.2 in linear and semi-log formats. The individual subject data, also presented in linear and semi-log formats, is displayed in Figures 3.3 through 3.83.

Figures 3.84 through 3.87 present the plots of the plasma diltiazem concentrations in linear format for all subjects in the test and reference groups.

Pharmacokinetic Parameters for Each Subject

Tables 3.3 and 3.4 report the N-desmethyldiltiazem pharmacokinetic parameters for each subject according to regimen.

Area Under the Plasma N-Desmethyldiltiazem Concentration-Time Curve (0 - t hours)

The area under the plasma N-desmethyldiltiazem concentration-time curve (0 - t hours) was calculated for each subject and regimen (Table 3.5). The arithmetic means (\pm SD) are presented below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
AUC(0-t hours)(ng·hr/mL)	929.36 \pm 285.08	1014.65 \pm 325.54

The ANOVA was performed on the log-transformed AUC (0 - t hours) data (Table 3.6). The 90% geometric confidence interval, ratio of means, and intra-subject coefficient of variation were also determined, based on pair-wise comparisons of the AUC (0 - t hours) data. The results are presented in Table 3.7 and are reported below:

AUC (0 - t hours)	90% Geometric C.I.	Ratio of Means	Intra-Subject C.V.
CARTIA XT™ (A) vs. CARDIZEM® CD (B)	87.90 % - 96.42 %	92.06 %	9.94 %

The frequency distribution of the regimen differences and ratios of the AUC (0 - t hours) values among subjects are presented in Figures 3.A to 3.B.

Area Under the Plasma N-Desmethyldiltiazem Concentration-Time Curve (0 - infinity)

The AUC (0 - infinity) data for each subject and regimen was evaluated and is presented in Table 3.8. The arithmetic mean (\pm SD) for each regimen is presented overleaf:

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 STUDY # 2443 (B01-527PK-DILG12)

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
AUC (0 - infinity) (ng·hr/mL)	1042.92 ± 325.60	1144.95 ± 381.10

The ANOVA was performed on the log-transformed AUC (0 - infinity) data (Table 3.9). The 90% geometric confidence interval, ratio of means, and intra-subject coefficient of variation were also determined, based on the pair-wise comparisons of the AUC (0 - infinity) data. The results are presented in Table 3.10 and are reported below:

AUC (0 - infinity)	90% Geometric C.I.	Ratio of Means	Intra-Subject C.V.
CARTIA XT™ (A) vs. CARDIZEM® CD (B)	87.65 % - 96.07 %	91.76 %	9.86 %

The frequency distribution of the regimen differences and ratios of the AUC (0 - infinity) values among subjects are presented in Figures 3.C to 3.D.

Peak Plasma N-Desmethyldiltiazem Concentrations

The peak, or maximal, plasma N-desmethyldiltiazem concentrations were determined for each subject and regimen (Table 3.11). The arithmetic means (\pm SD) were calculated and are presented below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
C_{max} (ng/mL)	35.22 ± 9.07	37.23 ± 11.01

The ANOVA was performed on the log-transformed C_{max} data (Table 3.12). The 90% geometric confidence interval, ratio of means, and intra-subject coefficient of variation were also determined, based on the pair-wise comparisons of the C_{max} data. The results are reported in Table 3.13 and are presented overleaf:

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 STUDY # 2443 (B01-527PK-DILG12)

C_{max}	90% Geometric C.I.	Ratio of Means	Intra-Subject C.V.
CARTIA XT™ (A) vs. CARDIZEM® CD (B)	90.25 % - 101.17 %	95.55 %	12.27 %

The frequency distribution of the regimen differences and ratios of the C_{max} values among subjects are presented in Figures 3.E to 3.F.

Time to Reach Peak Plasma N-Desmethyldiltiazem Concentrations

The time to reach peak plasma N-desmethyldiltiazem concentrations was determined for each subject and regimen (Table 3.14). The arithmetic means (\pm SD) are presented below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
T_{max} (hours)	15.04 \pm 3.66	15.07 \pm 5.12

The ANOVA was performed on the T_{max} (Table 3.15).

The Apparent Half-Life and Elimination Rate Constant of Plasma N-Desmethyldiltiazem

Table 3.16 presents the apparent half-life of plasma N-desmethyldiltiazem for each subject and regimen. The arithmetic means (\pm SD) were calculated and are presented below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
$t_{1/2}$ (hours)	10.93 \pm 2.33	10.96 \pm 1.84

Table 3.17 reports the results of the ANOVA performed on the $t_{1/2}$ data.

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
STUDY # 2443 (B01-527PK-DILG12)

The elimination rate constant of plasma N-desmethyldiltiazem was calculated for each subject and regimen, and the results are presented in Table 3.18. The arithmetic means (\pm SD) are reported below:

	CARTIA XT™ (A) 1 x 300 mg	CARDIZEM® CD (B) 1 x 300 mg
K_{el} (hour ⁻¹)	0.066 \pm 0.012	0.065 \pm 0.011

The ANOVA was performed on the K_{el} data (Table 3.19). The correlation coefficient (r value) of the most linear portion of the terminal elimination phase was also determined for each subject and regimen (Table 3.20).

CONCLUSIONS

The 90% geometric confidence intervals for diltiazem AUC_{0-t} , AUC_{0-inf} and C_{max} were 82.23 – 95.01%, 82.89 – 95.36% and 73.84 – 89.37%, respectively, with point estimates of 88.39%, 88.90% and 81.23% respectively. The test product therefore failed to demonstrate bioequivalence to the reference product. Metabolite data are provided as additional information.

TABLES &
FIGURES

SECTION 1.0: PLASMA DILTIAZEM

TABLES

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 1.

PLASMA DILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF ONE (1) CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg CAPSULE
 (Andrx Pharmaceuticals, Inc. (A), Lot Number: 600A073, Expiry Date: 07/02)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION											
	0.00	1.00	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00	11.00
01	N.Q.	N.Q.	4.470	16.363	77.158	159.947	133.999	108.506	92.254	80.176	112.259	114.315
03	N.Q.	N.Q.	N.Q.**	8.272	10.983	78.437	130.331	128.083	125.449	118.265	81.561	105.299
04	N.Q.	4.675**	7.658	10.410	18.896	94.598	104.958	106.825	94.444	82.378	80.029	86.179
05	N.Q.	N.Q.	6.215	16.717	59.764	105.503	108.486	92.718	94.426	91.887	87.764	104.973
06	N.Q.	N.Q.	N.Q.	4.899	11.768	39.312	63.657	65.388	80.246	67.455	54.392	51.038
07	N.Q.	N.Q.	4.016	30.845	178.120	217.230	160.683	132.884	111.030	97.958	102.247	101.539
08	N.Q.	N.Q.	N.Q.	N.Q.	3.018	25.740	61.212	61.305	57.457	53.686	42.901	35.713
09	N.Q.	N.Q.	6.810	7.296	15.001	60.871	145.469	144.120	160.220	159.393	129.751	118.618
10	N.Q.	N.Q.	N.Q.	N.Q.	5.639	67.764	66.461	45.626	38.088	29.430	24.248	22.126
11	N.Q.	N.Q.	4.919	13.669	98.553	178.833	189.968	155.606	135.505	121.257	101.119	94.430
12	N.Q.	N.Q.	N.Q.	N.Q.	9.228	51.105	53.634	44.723	40.984	36.034	34.463	37.315
13	N.Q.	N.Q.	N.Q.	7.953	39.014	71.460	62.624	49.383	44.266	35.932	30.702	29.588
14	N.Q.	N.Q.	7.591	80.809	118.299	123.494	120.043	98.640	88.374	88.627	106.645	109.461
15	N.Q.	N.Q.	N.Q.	5.666	25.062	35.159	33.976	32.748	31.128	29.747	36.430	38.639
16	N.Q.	N.Q.	N.Q.	12.586	48.690	52.731	47.093	56.643	49.701	42.634	36.858	33.420**
17	N.Q.	N.Q.	N.Q.	5.091	46.269	113.709	118.719	101.817	85.887	73.499	72.587	70.026
18	N.Q.	N.Q.	N.Q.	3.832	7.859	21.317	45.273	73.163	73.375	66.851	60.678	55.368
19	N.Q.	N.Q.	5.541	10.989	74.415	180.297	180.683	149.660	131.862	127.680	127.438	115.948
20	N.Q.	N.Q.	N.Q.	5.277	7.120	46.627	77.196	71.865	71.694	71.514	69.761	67.189
21	N.Q.	N.Q.	N.Q.	4.512	35.640	85.536	79.745	65.190	58.103	45.260	38.963	42.956
22	N.Q.	N.Q.	N.Q.	15.066**	30.262	56.158	59.101	68.132	65.046	68.574	63.150	60.753
23	N.Q.	N.Q.	6.210	8.523	11.653	47.479	93.490	103.923	101.999	93.600	71.363	57.958
24	N.Q.	N.Q.	5.086	10.634	14.884	47.335	75.498	98.844	103.950	97.779	98.371	96.928
25	N.Q.	N.Q.	4.013	5.330	12.973	40.157	52.221	56.401	58.314	51.864	48.406	52.922
26	N.Q.	N.Q.	N.Q.	4.011	8.239	35.345	62.087	67.246	62.285	59.328	48.135	46.144
27	N.Q.	N.Q.	N.Q.	4.581	10.801	142.996	183.929	178.324	144.553	110.926	88.079	92.075
28	N.Q.	N.Q.	N.Q.	3.202	9.338	51.767	71.053	75.263	82.643	70.253	76.796	65.479
MEAN	0.000*	0.173*	2.316*	10.983*	36.617	82.626	95.614	90.112	84.566	76.740	71.300	70.607
SD(±)	0.000*	0.900*	2.961*	15.398*	41.612	53.047	46.101	38.260	34.276	32.581	30.282	30.657
C.V.(%)	0.000*	519.615*	127.870*	140.203*	113.643	64.202	48.215	42.459	40.531	42.456	42.472	43.419
Range (Min.)	0.000*	0.000*	0.000*	0.000*	3.018	21.317	33.976	32.748	31.128	29.430	24.248	22.126
Range (Max.)	0.000	4.675	7.658	80.809	178.120	217.230	189.968	178.324	160.220	159.393	129.751	118.618
N =	27	27	27	27	27	27	27	27	27	27	27	27

Limit of quantitation = 3.010 ng/mL

N.Q. = Not quantifiable N.D. = No Data N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.Q.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
Study # 2443 (B01-527PK-DILG12)
TABLE 1. 1. (Continued)

PLASMA DILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF ONE (1) CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg CAPSULE
(Andrx Pharmaceuticals, Inc. (A), Lot Number: 600A073, Expiry Date: 07/02)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION										
	12.00	13.00	14.00	15.00	16.00	18.00	24.00	30.00	36.00	42.00	48.00
01	92.996	104.288	114.319	117.517	126.188	105.772	72.565	46.938	26.806	17.896	10.151
03	127.069	153.415	179.940**	205.863	196.609	230.501	177.614**	115.689	57.084	29.231	26.948
04	93.178**	115.650	157.152	149.063	156.766**	135.060	91.213	65.439	44.299**	28.588	19.318**
05	118.352	126.408	143.035	142.520	135.627	126.888	66.769	46.362	25.909	15.207	8.152
06	57.766	61.684	74.623	74.002	80.848	73.520	51.807	38.592	30.414	23.175	15.759
07	113.589	126.309	140.711	147.665	152.841	126.982	87.110	62.542	35.971	21.316	12.310
08	32.399	32.099	38.033	39.195	40.410	37.245	21.558	16.571	6.717	3.219	N.Q.
09	125.241	135.457	156.075	155.977	158.874	138.993	104.014	65.959	36.424	19.539	8.896
10	28.987	34.965	40.095	46.093	41.515	37.435	20.384	11.025	5.385	N.Q.	N.Q.
11	95.866	110.652	122.647	140.585	133.143	124.679	84.330	55.757	29.434	19.684	10.507
12	49.940	59.867	69.608	64.118	63.674	57.332	36.335	23.823	12.326	5.048	N.Q.
13	30.138	33.239	36.163	34.358	35.883	31.962	26.054	13.473	6.941	N.Q.	N.Q.
14	111.682	117.169	135.574	128.852	127.005	103.055	75.276	48.820	31.464	18.825	11.056
15	45.721	56.011	58.356	56.810	55.552	43.689	33.176	24.843	15.585	8.840	5.708
16	34.931	41.150	50.633	50.233	51.556	50.938	36.464	20.367	11.586	6.314	3.104
17	91.832	109.025	119.176	122.457	111.954	91.550	57.747	35.136	23.606	12.596	6.151
18	57.707	64.568	71.481	90.790	92.693	90.607	67.084	46.580	25.208	13.890	7.380**
19	113.997	111.434	113.088	124.303	135.842	125.252	100.695	74.385	70.226	34.224	19.741
20	75.126	91.326	104.830	110.617	107.097	112.110	65.469	37.901	17.687	10.556	5.917
21	53.127	74.313	82.051	92.903	87.625	76.194	46.249	23.168	12.946	6.411	4.520
22	63.490	72.813	74.414	73.527	70.408	72.041**	44.885	35.006	23.283	13.830	7.474
23	54.214	62.509	70.966	79.831	87.819	81.741	55.889	44.745	27.894	16.814	9.879
24	105.626	128.780	148.968	157.976	168.105	164.115	105.632	68.939	44.790	29.031	20.615
25	61.551	79.971	97.584	102.637	100.791	77.791	56.435	33.899	16.999	8.801	4.296
26	45.280	54.007	78.195	98.824	95.104	83.507	55.265	27.854	13.647	8.421	3.756
27	96.084	110.111	140.078	151.458	155.187	137.739	84.185	59.826	37.751	20.032	9.350
28	62.138	66.503**	61.300	71.255	73.468**	64.272	50.680	30.653	23.528	15.799	10.780
MEAN	75.482	86.434	99.226	104.794	105.281	96.332	65.736	43.492	26.441	15.085*	8.954*
SD (±)	31.698	35.024	41.463	43.635	43.877	44.852	33.216	22.956	15.408	9.072*	6.822*
C.V. (%)	41.994	40.521	41.787	41.639	41.677	46.559	50.528	52.782	58.273	60.140*	76.183*
Range (Min.)	28.987	32.099	36.163	34.358	35.883	31.962	20.384	11.025	5.385	0.000*	0.000*
(Max.)	127.069	153.415	179.940	205.863	196.609	230.501	177.614	115.689	70.226	34.224	26.948
N =	27	27	27	27	27	27	27	27	27	27	27

Limit of quantitation = 3.010 ng/mL

N.Q. = Not quantifiable N.D. = No Data N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.Q.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 2.

PLASMA DILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF 1 x 300 CARDIZEM[®] CD (DILTIAZEM HCl) CAPSULE
 (Aventis Pharmaceuticals, Inc. (B), Lot Number: 1030455, Expiry Date: 11/2002)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION											
	0.00	1.00	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00	11.00
01	N.Q.	N.Q.	N.Q.	13.868	107.408	307.910	252.540	152.982	143.762	110.719	126.851	138.775
03	N.Q.	N.Q.	N.Q.	N.Q.	14.657	161.542	185.323	147.691	104.329	49.501	62.624	46.822
04	N.Q.	N.Q.	N.Q.	7.702	83.256	277.770	177.210	184.554	129.561	98.920	85.168	67.309
05	N.Q.	N.Q.	N.Q.	3.325	89.697	157.788	128.154	108.055	83.546	73.510	67.279	60.466
06	N.Q.	N.Q.	N.D.	N.Q.	22.901	133.053	117.577	82.911	58.745	45.029	38.953	31.491
07	N.Q.	N.Q.	N.Q.	6.147	80.246	147.750	107.243	91.000	79.343	76.070	72.626	77.750
08	N.Q.	N.Q.	N.Q.	N.Q.	8.291	93.228	91.218	80.003	50.683	41.229	30.044	23.511
09	N.Q.	N.Q.	N.Q.	60.014	244.589	203.759	168.535	148.870	141.405	141.704	175.224	182.108
10	N.Q.	N.Q.	N.Q.	N.Q.	13.960	67.204	59.127	40.676	34.144	26.609	18.267	12.884
11	N.Q.	N.Q.	N.Q.	6.988	145.888	217.186	181.274	142.211	122.213	117.618	104.074	105.626
12	N.Q.	N.Q.	N.Q.	N.Q.	8.546	55.902	80.318	69.661	46.203	37.230	30.578	25.661
13	N.Q.	N.Q.	N.Q.	N.Q.	9.640	51.365	63.716	60.728	48.197	45.622	44.807	45.731
14	N.Q.	N.Q.	N.Q.	N.Q.	70.569	209.567	187.034	161.811	136.567	114.043	121.990	132.510
15	N.Q.	N.Q.	N.Q.	4.040	83.086	59.817	62.248	59.685	50.897	51.048	60.413	71.840
16	N.Q.	N.Q.	N.Q.	N.Q.	51.274	69.622	52.436	45.772	40.982	44.444	49.308	52.293
17	N.Q.	N.Q.	N.Q.	N.Q.	5.265	80.202	91.045	71.998	66.115	52.754	46.286	42.372
18	N.Q.	N.Q.	N.Q.	N.Q.	21.299	106.138	90.737	64.498	54.614	40.412	34.298	28.483
19	N.Q.	N.Q.	N.Q.	N.Q.	18.085	177.229	192.408	139.556	105.827	95.222	69.864	62.008
20	N.Q.	N.Q.	N.Q.	N.Q.	5.619	47.826	75.338	74.713	67.658	60.082	65.848	62.307
21	N.Q.	N.Q.	N.Q.	N.Q.	18.693	62.008	93.104	74.103	55.749	43.078	31.909	25.730
22	N.Q.	N.Q.	N.Q.	N.Q.	17.699	112.719	108.178	83.515	70.549	63.796	48.966	40.731
23	N.Q.	N.Q.	N.Q.	7.315	143.711	188.015**	127.293	112.124	79.451	61.261	50.115	42.858
24	N.Q.	N.Q.	N.Q.	N.Q.	61.131	226.703	227.920	184.151	140.514	97.097	98.924	80.261
25	N.Q.	N.Q.	N.Q.	N.Q.	52.385	113.629	88.326	63.110	49.587	45.607	39.626	41.377
26	N.Q.	N.Q.	N.Q.	N.Q.	59.278	122.486	103.303	90.628	72.684	60.729	56.765	66.270
27	N.Q.	N.Q.	N.Q.	N.Q.	35.245	174.377	161.899	122.808	94.205	81.390	68.225	75.939
28	N.Q.	N.Q.	N.Q.	N.Q.	45.555	116.452	94.642	83.364	69.692	51.878	43.922	36.736
MEAN	0.000*	0.000*	0.000*	4.052*	56.221	138.565	124.746	101.525	81.379	67.652	64.554	62.217
SD(±)	0.000*	0.000*	0.000*	11.730*	55.424	70.890	54.663	42.158	34.556	29.612	35.286	39.005
C.V.(%)	0.000*	0.000*	0.000*	289.506*	98.582	51.160	43.820	41.525	42.464	43.771	54.661	62.692
Range (Min.)	0.000*	0.000*	0.000*	0.000*	5.265	47.826	52.436	40.676	34.144	26.609	18.267	12.884
(Max.)	0.000	0.000	0.000	60.014	244.589	307.910	252.540	184.554	143.762	141.704	175.224	182.108
N =	27	27	26	27	27	27	27	27	27	27	27	27

Limit of quantitation = 3.010 ng/mL

N.Q. = Not quantifiable N.D. = No Data N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.Q.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 2. (Continued)

PLASMA DILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF 1 x 300 CARDIZEM[®] CD (DILTIAZEM HCl) CAPSULE
 (Aventis Pharmaceuticals, Inc. (E), Lot Number: 1030455, Expiry Date: 11/2002)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION										
	12.00	13.00	14.00	15.00	16.00	18.00	24.00	30.00	36.00	42.00	48.00
01	153.685	204.592	232.504	209.280	174.115	150.434	94.569	63.234	36.515	19.942	7.094**
03	42.826	62.691	106.575	161.239	181.231	241.207	163.675	130.436	67.821	42.574	29.313
04	75.746	72.448**	96.347	126.628**	95.148**	141.226	154.730	115.840	78.205	46.926**	26.684**
05	79.860	84.884	111.165	120.539	126.627	121.801	93.645	86.177	44.910	21.957	13.285
06	37.392	38.815	45.280	54.086	69.738	79.318	87.460	53.439	31.517	17.372	10.096
07	90.640	98.972	110.860	115.325	106.952	108.848	69.415	49.060	29.539	16.617	9.057
08	21.520	26.794	38.357	50.825	52.028	53.900	35.409	28.883	15.208	8.724	4.379
09	181.036	190.919	213.459	213.163	196.560	165.273	92.610	51.029	26.542	14.011	6.912
10	16.463	31.714	54.500	63.238	61.569	51.689	23.496	14.460	7.363	3.518	N.Q.
11	122.975	160.072	193.626	212.713	191.599	185.346	141.442	94.039	63.800	40.322	21.658
12	25.261	27.901	35.734	39.534	41.295	38.625	27.022	17.703	8.603	4.580	N.Q.
13	43.395	44.541	47.051	50.110	48.129	44.236	36.667	25.561	13.998	6.029	3.021
14	180.241	214.486	235.940	237.808	232.122	204.440	151.190	98.948	59.588	37.185	20.894
15	67.652	71.234	70.406	65.498	61.376	48.745	39.098	26.354**	14.517	8.966	6.136
16	54.596	57.877	61.225	53.040	57.429	54.025	40.691	23.465	11.346	6.491	4.116
17	44.014	54.268	67.548	75.371	76.303	75.765	50.847	39.570**	22.394	14.400	7.418
18	26.786	29.813	37.166	46.658	59.917	64.652	71.405	50.119	28.391	15.641	7.481
19	74.574	105.775	130.079	153.721	162.748	167.661	118.957	84.034	60.784	38.545	20.119
20	59.621	77.781	92.788	92.534	94.575	81.477	73.426	40.512	19.904	12.741	6.695
21	22.579	34.750	61.690	70.738	74.285	73.008	50.682	28.075	17.755	9.870	7.390
22	56.149	72.963	86.405	104.380	112.745	101.318	66.227	51.839	33.964	19.214	10.660
23	49.188	61.088	64.600	64.977	69.453	84.598	71.128	50.994	32.644	20.863	12.466
24	78.670	90.094	116.927	142.093	172.911	194.328	135.756	84.548	58.136	29.612	23.529
25	49.298	63.393	76.372	85.341	82.864	72.063	50.696	30.976	16.258	8.597	4.542
26	93.890	112.610	131.426	160.375	179.904	105.443	73.251	37.811	17.669	9.666	4.967
27	85.248**	99.041	106.618	132.339	124.169**	137.648	89.952	63.276	35.384	25.981	16.595
28	38.768	46.566	61.008	70.601	85.044	101.373	72.415	42.191	22.607	13.721	7.716
MEAN	69.336	82.818	99.469	110.080	110.772	109.202	80.587	54.910	32.421	19.039	10.823*
SD(±)	44.993	53.159	58.311	58.924	55.379	55.560	40.673	30.624	20.024	12.508	8.023*
C.V.(%)	64.891	64.188	58.623	53.528	49.994	50.878	50.470	55.771	61.762	65.693	74.131*
Range (Min.)	16.463	26.794	35.734	39.534	41.295	38.625	23.496	14.460	7.363	3.518	0.000*
(Max.)	181.036	214.486	235.940	237.808	232.122	241.207	163.675	130.436	78.205	46.926	29.313
N =	27	27	27	27	27	27	27	27	27	27	27

Limit of quantitation = 3.010 ng/mL

N.Q. = Not quantifiable

N.D. = No Data

N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.Q.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 3.

SUMMARY OF DILTIAZEM PARAMETERS FOR EACH SUBJECT GIVEN THE ONE (1) CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg CAPSULE
 (Andrx Pharmaceuticals, Inc. (A), Lot Number: 600A073, Expiry Date: 07/02)

SUBJECT	SEQ	PERIOD	C _{max} (ng/mL)	T _{max} (hrs)	AUC(0-t) (ng.hr/mL)	AUC(0-inf) (ng.hr/mL)	AUC(0-t)		K _{el} (hr ⁻¹)	T _{half} (hrs)
							----- (%)	AUC(0-inf)		
01	AB	1	159.95	5.00	2956.62	3080.97	95.96	0.082	8.49	
03	AB	1	230.50	18.00	5028.82	5342.78	94.12	0.086	8.08	
04	BA	2	157.15	14.00	3417.24	3700.23	92.35	0.068	10.15	
05	BA	2	143.04	14.00	2959.70	3044.80	97.21	0.096	7.24	
06	BA	2	80.85	16.00	2032.79	2352.47	86.41	0.049	14.06	
07	BA	2	217.23	5.00	3680.58	3817.37	96.42	0.090	7.70	
08	AB	1	61.31	7.00	971.09	1004.64	96.66	0.096	7.23	
09	BA	2	160.22	8.00	3696.89	3777.36	97.87	0.111	6.27	
10	AB	1	67.76	5.00	866.14	916.38	94.52	0.107	6.47	
11	AB	1	189.97	6.00	3428.79	3549.87	96.59	0.087	7.99	
12	AB	1	69.61	14.00	1325.91	1371.93	96.65	0.110	6.32	
13	BA	2	71.46	5.00	944.48	1030.06	91.69	0.081	8.55	
14	AB	1	135.57	14.00	3117.47	3250.96	95.89	0.083	8.37	
15	AB	1	58.36	14.00	1255.33	1324.11	94.81	0.083	8.35	
16	BA	2	56.64	7.00	1296.10	1326.64	97.70	0.102	6.82	
17	AB	1	122.46	15.00	2457.19	2527.13	97.23	0.088	7.88	
18	AB	1	92.69	16.00	2132.62	2204.99	96.72	0.102	6.80	
19	BA	2	180.68	6.00	4008.51	4339.28	92.38	0.060	11.61	
20	AB	1	112.11	18.00	2286.66	2344.99	97.51	0.101	6.83	
21	AB	1	92.90	15.00	1740.72	1786.72	97.43	0.098	7.05	
22	AB	1	74.41	14.00	1887.91	1974.93	95.59	0.086	8.07	
23	BA	2	103.92	7.00	2224.10	2341.76	94.98	0.084	8.26	
24	BA	2	168.11	16.00	3651.47	3946.40	92.53	0.070	9.92	
25	BA	2	102.64	15.00	1896.39	1933.99	98.06	0.114	6.07	
26	BA	2	98.82	15.00	1788.20	1822.48	98.12	0.110	6.33	
27	BA	2	183.93	6.00	3476.55	3567.00	97.46	0.103	6.71	
28	BA	2	82.64	8.00	1890.65	2069.06	91.38	0.060	11.47	
MEAN			121.29	11.22	2459.96	2583.31	95.34	0.09	8.11	
SD(±)			51.30	4.70	1086.85	1151.26	2.73	0.02	1.90	
C.V. (%)			42.29	41.89	44.18	44.57	2.86	18.99	23.37	
Range (Min.)			56.64	5.00	866.14	916.38	86.41	0.05	6.07	
(Max.)			230.50	18.00	5028.82	5342.78	98.12	0.11	14.06	
Num of subjects			27	27	27	27	27	27	27	

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 4.

SUMMARY OF DILTIAZEM PARAMETERS FOR EACH SUBJECT GIVEN THE CARDIZEM® CD (DILTIAZEM HCl) CAPSULE
 (Aventis Pharmaceuticals, Inc. (B), Lot Number: 1030455, Expiry Date: 11/2002)

SUBJECT	SEQ	PERIOD	C _{max} (ng/mL)	T _{max} (hrs)	AUC(0-t) (ng.hr/mL)	AUC(0-inf) (ng.hr/mL)	AUC(0-t)	K _{el} (hr ⁻¹)	T _{half} (hrs)
							-----(%) AUC(0-inf)		
01	AB	2	307.91	5.00	4324.85	4384.28	98.64	0.119	5.81
03	AB	2	241.21	18.00	4897.47	5253.20	93.23	0.082	8.41
04	BA	1	277.77	5.00	4644.91	4971.00	93.44	0.082	8.47
05	BA	1	157.79	5.00	3365.40	3491.43	96.39	0.105	6.58
06	BA	1	133.05	5.00	2297.13	2405.40	95.50	0.093	7.43
07	BA	1	147.75	5.00	2764.75	2861.04	96.63	0.094	7.37
08	AB	2	93.23	5.00	1391.83	1434.10	97.05	0.104	6.69
09	BA	1	244.59	4.00	4346.61	4409.10	98.58	0.111	6.27
10	AB	2	67.20	5.00	1020.36	1052.73	96.93	0.109	6.38
11	AB	2	217.19	5.00	4963.84	5246.34	94.62	0.077	9.04
12	AB	2	80.32	6.00	1032.68	1078.13	95.78	0.101	6.88
13	BA	1	63.72	6.00	1306.63	1331.64	98.12	0.121	5.74
14	AB	2	237.81	15.00	5312.66	5556.70	95.61	0.086	8.10
15	AB	2	83.09	4.00	1617.13	1694.10	95.46	0.080	8.69
16	BA	1	69.62	5.00	1439.42	1481.51	97.16	0.098	7.09
17	AB	2	91.05	6.00	1900.51	1981.90	95.89	0.091	7.60
18	AB	2	106.14	5.00	1945.16	2016.39	96.47	0.105	6.60
19	BA	1	192.41	6.00	4113.39	4408.72	93.30	0.068	10.17
20	AB	2	94.58	16.00	2149.47	2217.02	96.95	0.099	6.99
21	AB	2	93.10	6.00	1658.05	1750.33	94.73	0.080	8.65
22	AB	2	112.75	16.00	2499.88	2620.23	95.41	0.089	7.83
23	BA	1	188.02	5.02	2585.88	2745.91	94.17	0.078	8.90
24	BA	1	227.92	6.00	4500.06	4818.86	93.38	0.074	9.39
25	BA	1	113.63	5.00	1833.39	1875.99	97.73	0.107	6.50
26	BA	1	179.90	16.00	2667.36	2711.53	98.37	0.112	6.16
27	BA	1	174.38	5.00	3311.24	3545.37	93.40	0.071	9.78
28	BA	1	116.45	5.00	2220.99	2303.64	96.41	0.093	7.42
MEAN			152.32	7.22	2818.93	2949.87	95.90	0.09	7.59
SD(±)			70.88	4.41	1350.22	1434.92	1.70	0.01	1.24
C.V.(%)			46.53	61.11	47.90	48.64	1.77	15.87	16.29
Range (Min.)			63.72	4.00	1020.36	1052.73	93.23	0.07	5.74
(Max.)			307.91	18.00	5312.66	5556.70	98.64	0.12	10.17
Num of subjects			27	27	27	27	27	27	27

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 5.

AREA UNDER THE PLASMA DILTIAZEM CONCENTRATION-TIME CURVES (0-t hrs.)

SUBJECT No.	RAW SCALE			RATIO% #	LOG SCALE		
	CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg	DIFF		CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg	DIFF *
01	2956.62	4324.85	-1368.23	68.36	7.9918	8.3721	-0.3803
03	5028.82	4897.47	131.35	102.68	8.5229	8.4965	0.0265
04	3417.24	4644.91	-1227.67	73.57	8.1366	8.4435	-0.3069
05	2959.70	3365.40	-405.70	87.94	7.9928	8.1213	-0.1285
06	2032.79	2297.13	-264.34	88.49	7.6172	7.7394	-0.1223
07	3680.58	2764.75	915.83	133.13	8.2108	7.9247	0.2861
08	971.09	1391.83	-420.74	69.77	6.8784	7.2384	-0.3600
09	3696.89	4346.61	-649.72	85.05	8.2152	8.3772	-0.1619
10	866.14	1020.36	-154.22	84.89	6.7641	6.9279	-0.1639
11	3428.79	4963.84	-1535.05	69.08	8.1400	8.5099	-0.3700
12	1325.91	1032.68	293.23	128.39	7.1899	6.9399	0.2499
13	944.48	1306.63	-362.16	72.28	6.8506	7.1752	-0.3246
14	3117.47	5312.66	-2195.19	58.68	8.0448	8.5778	-0.5331
15	1255.33	1617.13	-361.81	77.63	7.1351	7.3884	-0.2533
16	1296.10	1439.42	-143.32	90.04	7.1671	7.2720	-0.1049
17	2457.19	1900.51	556.68	129.29	7.8068	7.5499	0.2569
18	2132.62	1945.16	187.45	109.64	7.6651	7.5731	0.0920
19	4008.51	4113.39	-104.88	97.45	8.2962	8.3220	-0.0258
20	2286.66	2149.47	137.19	106.38	7.7348	7.6730	0.0619
21	1740.72	1658.05	82.66	104.99	7.4621	7.4134	0.0487
22	1887.91	2499.88	-611.97	75.52	7.5432	7.8240	-0.2808
23	2224.10	2585.88	-361.78	86.01	7.7071	7.8578	-0.1507
24	3651.47	4500.06	-848.59	81.14	8.2029	8.4118	-0.2090
25	1896.39	1833.39	63.00	103.44	7.5477	7.5139	0.0338
26	1788.20	2667.36	-879.16	67.04	7.4890	7.8888	-0.3999
27	3476.55	3311.24	165.30	104.99	8.1538	8.1051	0.0487
28	1890.65	2220.99	-330.35	85.13	7.5447	7.7057	-0.1610
MEAN	2459.96	2818.93	-358.97	90.41	7.7041	7.8275	-0.1234
SD(±)	1086.85	1350.22	670.18	19.92	0.4812	0.5018	0.2152
C.V.(%)	44.18	47.90	186.70	22.04	6.2463	6.4108	174.3760
Range (Min.)	866.14	1020.36	-2195.19	58.68	6.7641	6.9279	-0.5331
(Max.)	5028.82	5312.66	915.83	133.13	8.5229	8.5778	0.2861
Num of subjects	27	27	27	27	27	27	27
Geometric Mean					2217.4208	2508.6499	

RATIO% = (CARTIA XTTM / CARDIZEM[®] CD) × 100

* DIFF(Log Scale) = ln(CARTIA XTTM) - ln(CARDIZEM[®] CD)

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 6.

ANOVA ON DILTIAZEM LOG AUC (0 - t hrs.)

The GLM Procedure

Dependent Variable: lauct

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	12.17152558	0.43469734	18.05	<.0001
Error	25	0.60207691	0.02408308		
Corrected Total	53	12.77360249			

R-Square	Coeff Var	Root MSE	lauct Mean
0.952866	1.998340	0.155187	7.765806

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.48144561	0.48144561	19.99	0.0001
subj (sq)	25	11.48445817	0.45937833	19.07	<.0001
peri	1	0.00000007	0.00000007	0.00	0.9986
drug	1	0.20534885	0.20534885	8.53	0.0073

The GLM Procedure
 Least Squares Means

drug	lauct LSMEAN	Standard Error	Pr > t
A	7.70059802	0.02988630	<.0001
B	7.82401569	0.02988630	<.0001

sq	lauct LSMEAN	Standard Error	Pr > t
AB	7.66781925	0.03043472	<.0001
BA	7.85679445	0.02932763	<.0001

peri	lauct LSMEAN	Standard Error	Pr > t
1	7.76226959	0.02988630	<.0001
2	7.76234411	0.02988630	<.0001

The GLM Procedure

Dependent Variable: lauct

Tests of Hypotheses Using the Type III MS for subj (sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.48144561	0.48144561	1.05	0.3158

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	-0.12341767	0.04226561	-2.92	0.0073

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 7.

90% GEOMETRIC CONFIDENCE INTERVAL BASED ON AREA UNDER THE PLASMA DILTIAZEM
 CONCENTRATION-TIME CURVES

LOG AUC (0-t) (ng.hr/mL)

Source	DF	TYPE III SS	Mean Square	F Value	Pr > F
ERROR	25	0.602077	0.024083		
sq	1	0.481446	0.481446	19.991034	0.000147
subj(sq)	25	11.484458	0.459378	19.074736	0.000000
peri	1	0.000000	0.000000	0.000003	0.998607
drug	1	0.205349	0.205349	8.526687	0.007311

$$\text{INTRA-SUBJECT C.V.} = 100 \times \text{SQRT}(\text{MSE}) = 100 \times \text{SQRT}(0.024083) = 15.52 \%$$

$$\text{DIFFERENCE} = \text{TEST} - \text{REFERENCE} = 7.700598 - 7.824016 = -.123418$$

$$\text{SE DIFFERENCE} = 0.042266$$

$$\text{AUC}(0-t) \text{ RATIO} = 100 \times e^{\frac{(\text{difference})}{\text{SE DIFFERENCE}}} = 100 \times e^{\frac{(7.700598 - 7.824016)}{0.042266}} = 88.39 \%$$

90% GEOMETRIC CONFIDENCE INTERVAL

$$\text{LOWER, UPPER} = 100 \times e^{(\text{difference} \pm t_{0.05, 25} \times \text{SE difference})}$$

$$\text{LOWER} = 100 \times e^{(-.123418 - 1.7081 \times 0.042266)} = 82.23 \%$$

$$\text{UPPER} = 100 \times e^{(-.123418 + 1.7081 \times 0.042266)} = 95.01 \%$$

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 8.

AREA UNDER THE PLASMA DILTIAZEM CONCENTRATION-TIME CURVES (0 - infinity)

AUC (0-inf) (ng.hr/mL)

SUBJECT No.	RAW SCALE			RATIO% #	LOG SCALE		
	CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg	DIFF		CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg	DIFF *
01	3080.97	4384.28	-1303.31	70.27	8.0330	8.3858	-0.3528
03	5342.78	5253.20	89.59	101.71	8.5835	8.5666	0.0169
04	3700.23	4971.00	-1270.77	74.44	8.2161	8.5114	-0.2952
05	3044.80	3491.43	-446.63	87.21	8.0212	8.1581	-0.1369
06	2352.47	2405.40	-52.93	97.80	7.7632	7.7855	-0.0223
07	3817.37	2861.04	956.33	133.43	8.2473	7.9589	0.2884
08	1004.64	1434.10	-429.46	70.05	6.9124	7.2683	-0.3559
09	3777.36	4409.10	-631.74	85.67	8.2368	8.3914	-0.1546
10	916.38	1052.73	-136.35	87.05	6.8204	6.9591	-0.1387
11	3549.87	5246.34	-1696.47	67.66	8.1747	8.5653	-0.3906
12	1371.93	1078.13	293.81	127.25	7.2240	6.9830	0.2410
13	1030.06	1331.64	-301.58	77.35	6.9374	7.1942	-0.2568
14	3250.96	5556.70	-2305.74	58.51	8.0867	8.6228	-0.5361
15	1324.11	1694.10	-369.99	78.16	7.1885	7.4349	-0.2464
16	1326.64	1481.51	-154.87	89.55	7.1904	7.3008	-0.1104
17	2527.13	1981.90	545.24	127.51	7.8348	7.5918	0.2430
18	2204.99	2016.39	188.61	109.35	7.6985	7.6091	0.0894
19	4339.28	4408.72	-69.44	98.42	8.3755	8.3913	-0.0159
20	2344.99	2217.02	127.97	105.77	7.7600	7.7039	0.0561
21	1786.72	1750.33	36.39	102.08	7.4881	7.4676	0.0206
22	1974.93	2620.23	-645.30	75.37	7.5883	7.8710	-0.2827
23	2341.76	2745.91	-404.15	85.28	7.7587	7.9179	-0.1592
24	3946.40	4818.86	-872.46	81.89	8.2806	8.4803	-0.1997
25	1933.99	1875.99	58.00	103.09	7.5673	7.5369	0.0304
26	1822.48	2711.53	-889.05	67.21	7.5080	7.9053	-0.3973
27	3567.00	3545.37	21.64	100.61	8.1795	8.1734	0.0061
28	2069.06	2303.64	-234.58	89.82	7.6348	7.7422	-0.1074
MEAN	2583.31	2949.87	-366.57	90.83	7.7522	7.8695	-0.1173
SD(±)	1151.26	1434.92	693.12	19.28	0.4821	0.5089	0.2090
C.V.(%)	44.57	48.64	189.08	21.22	6.2184	6.4667	178.1992
Range (Min.)	916.38	1052.73	-2305.74	58.51	6.8204	6.9591	-0.5361
(Max.)	5342.78	5556.70	956.33	133.43	8.5835	8.6228	0.2884
Num of subjects	27	27	27	27	27	27	27
Geometric Mean					2326.6855	2616.2571	

RATIO% = (CARTIA XTTM / CARDIZEM[®] CD) × 100

* DIFF(Log Scale) = ln(CARTIA XTTM) - ln(CARDIZEM[®] CD)

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 9.

ANOVA ON DILTIAZEM LOG AUC (0 - inf)

The GLM Procedure

Dependent Variable: lauci

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	12.39399314	0.44264261	19.52	<.0001
Error	25	0.56704699	0.02268188		
Corrected Total	53	12.96104013			

R-Square	Coeff Var	Root MSE	lauci Mean
0.956250	1.928150	0.150605	7.810858

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.52494154	0.52494154	23.14	<.0001
subj(sq)	25	11.68239426	0.46729577	20.60	<.0001
peri	1	0.00091909	0.00091909	0.04	0.8421
drug	1	0.18645188	0.18645188	8.22	0.0083

The GLM Procedure
 Least Squares Means

drug	lauci LSMEAN	Standard Error	Pr > t
A	7.74840318	0.02900385	<.0001
B	7.86600515	0.02900385	<.0001

sq	lauci LSMEAN	Standard Error	Pr > t
AB	7.70854063	0.02953608	<.0001
BA	7.90586770	0.02846168	<.0001

peri	lauci LSMEAN	Standard Error	Pr > t
1	7.80307577	0.02900385	<.0001
2	7.81133256	0.02900385	<.0001

The GLM Procedure

Dependent Variable: lauci

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.52494154	0.52494154	1.12	0.2993

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	-0.11760196	0.04101764	-2.87	0.0083

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 10.

90% GEOMETRIC CONFIDENCE INTERVAL BASED ON AREA UNDER THE PLASMA DILTIAZEM
 CONCENTRATION-TIME CURVES

LOG AUC (0-inf) (ng.hr/mL)

Source	DF	TYPE III SS	Mean Square	F Value	Pr > F
ERROR	25	0.567047	0.022682		
sq	1	0.524942	0.524942	23.143653	0.000061
subj (sq)	25	11.682394	0.467296	20.602163	0.000000
peri	1	0.000919	0.000919	0.040521	0.842094
drug	1	0.186452	0.186452	8.220301	0.008290

INTRA-SUBJECT C.V. = $100 \times \text{SQRT}(\text{MSE}) = 100 \times \text{SQRT}(0.022682) = 15.06 \%$

DIFFERENCE = TEST - REFERENCE = $7.748403 - 7.866005 = -.117602$

SE DIFFERENCE = 0.041018

AUCINF RATIO = $100 \times e^{\frac{(\text{difference})}{\text{SE DIFFERENCE}}} = 100 \times e^{\frac{(7.748403 - 7.866005)}{0.041018}} = 88.90 \%$

90% GEOMETRIC CONFIDENCE INTERVAL

LOWER, UPPER = $100 \times e^{(\text{difference} \pm t_{0.05, 25} \times \text{SE difference})}$

LOWER = $100 \times e^{(-.117602 - 1.7081 \times 0.041018)} = 82.89 \%$

UPPER = $100 \times e^{(-.117602 + 1.7081 \times 0.041018)} = 95.36 \%$

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 11.

PEAK PLASMA DILTIAZEM CONCENTRATIONS

 C_{max} (ng/mL)

SUBJECT No.	RAW SCALE			RATIO% #	LOG SCALE		
	CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg	DIFF		CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg	DIFF *
01	159.95	307.91	-147.96	51.95	5.0748	5.7298	-0.6550
03	230.50	241.21	-10.71	95.56	5.4403	5.4857	-0.0454
04	157.15	277.77	-120.62	56.58	5.0572	5.6268	-0.5696
05	143.04	157.79	-14.75	90.65	4.9631	5.0613	-0.0982
06	80.85	133.05	-52.21	60.76	4.3926	4.8907	-0.4982
07	217.23	147.75	69.48	147.03	5.3810	4.9955	0.3854
08	61.31	93.23	-31.92	65.76	4.1159	4.5350	-0.4192
09	160.22	244.59	-84.37	65.51	5.0765	5.4996	-0.4230
10	67.76	67.20	0.56	100.83	4.2160	4.2077	0.0083
11	189.97	217.19	-27.22	87.47	5.2469	5.3808	-0.1339
12	69.61	80.32	-10.71	86.67	4.2429	4.3860	-0.1431
13	71.46	63.72	7.74	112.15	4.2691	4.1544	0.1147
14	135.57	237.81	-102.23	57.01	4.9095	5.4715	-0.5619
15	58.36	83.09	-24.73	70.24	4.0666	4.4199	-0.3533
16	56.64	69.62	-12.98	81.36	4.0368	4.2431	-0.2063
17	122.46	91.05	31.41	134.50	4.8078	4.5114	0.2964
18	92.69	106.14	-13.45	87.33	4.5293	4.6647	-0.1354
19	180.68	192.41	-11.72	93.91	5.1967	5.2596	-0.0629
20	112.11	94.58	17.53	118.54	4.7195	4.5494	0.1701
21	92.90	93.10	-0.20	99.78	4.5316	4.5337	-0.0022
22	74.41	112.75	-38.33	66.00	4.3096	4.7251	-0.4155
23	103.92	188.02	-84.09	55.27	4.6437	5.2365	-0.5929
24	168.11	227.92	-59.82	73.76	5.1246	5.4290	-0.3044
25	102.64	113.63	-10.99	90.33	4.6312	4.7329	-0.1017
26	98.82	179.90	-81.08	54.93	4.5933	5.1924	-0.5991
27	183.93	174.38	9.55	105.48	5.2145	5.1612	0.0533
28	82.64	116.45	-33.81	70.97	4.4145	4.7575	-0.3429
MEAN	121.29	152.32	-31.02	84.46	4.7113	4.9200	-0.2087
SD(±)	51.30	70.88	48.15	24.83	0.4274	0.4729	0.2856
C.V.(%)	42.29	46.53	155.22	29.40	9.0727	9.6116	136.8165
Range (Min.)	56.64	63.72	-147.96	51.95	4.0368	4.1544	-0.6550
(Max.)	230.50	307.91	69.48	147.03	5.4403	5.7298	0.3854
Num of subjects	27	27	27	27	27	27	27
Geometric Mean					111.1966	137.0026	

RATIO% = (CARTIA XT™ / CARDIZEM® CD) × 100

* DIFF(Log Scale) = ln(CARTIA XT™) - ln(CARDIZEM® CD)

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 12.

ANOVA ON DILTIAZEM LOG C_{max}

The GLM Procedure

Dependent Variable: lc_{max}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	10.10046422	0.36073087	8.57	<.0001
Error	25	1.05249769	0.04209991		
Corrected Total	53	11.15296191			

R-Square	Coeff Var	Root MSE	lc _{max} Mean
0.905631	4.260720	0.205183	4.815680

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.42599512	0.42599512	10.12	0.0039
subj(sq)	25	9.07851069	0.36314043	8.63	<.0001
peri	1	0.00775927	0.00775927	0.18	0.6714
drug	1	0.58240212	0.58240212	13.83	0.0010

The GLM Procedure
 Least Squares Means

drug	lc _{max} LSMEAN	Standard Error	Pr > t
A	4.70846447	0.03951452	<.0001
B	4.91631094	0.03951452	<.0001

sq	lc _{max} LSMEAN	Standard Error	Pr > t
AB	4.72350782	0.04023962	<.0001
BA	4.90126759	0.03877587	<.0001

peri	lc _{max} LSMEAN	Standard Error	Pr > t
1	4.82438302	0.03951452	<.0001
2	4.80039239	0.03951452	<.0001

The GLM Procedure

Dependent Variable: lc_{max}

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.42599512	0.42599512	1.17	0.2891

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	-0.20784647	0.05588198	-3.72	0.0010

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 13.

90% GEOMETRIC CONFIDENCE INTERVAL BASED ON THE LOG PEAK DILTIAZEM
 CONCENTRATION - LOG C_{max} (ng/mL)

Source	DF	TYPE III SS	Mean Square	F Value	Pr > F
ERROR	25	1.052498	0.042100	.	.
sq	1	0.425995	0.425995	10.118671	0.003893
subj (sq)	25	9.078511	0.363140	8.625682	0.000000
peri	1	0.007759	0.007759	0.184306	0.671376
drug	1	0.582402	0.582402	13.833810	0.001015

INTRA-SUBJECT C.V. = $100 \times \text{SQRT}(\text{MSE}) = 100 \times \text{SQRT}(0.042100) = 20.52 \%$

DIFFERENCE = TEST - REFERENCE = $4.708464 - 4.916311 = -.207846$

SE DIFFERENCE = 0.055882

C_{max} RATIO = $100 \times e^{(\text{difference})} = 100 \times e^{(4.708464 - 4.916311)} = 81.23 \%$

90% GEOMETRIC CONFIDENCE INTERVAL

LOWER, UPPER = $100 \times e^{(\text{difference} \pm t_{0.05, 25} \times \text{SE difference})}$

LOWER = $100 \times e^{(-.207846 - 1.7081 \times 0.055882)} = 73.84 \%$

UPPER = $100 \times e^{(-.207846 + 1.7081 \times 0.055882)} = 89.37 \%$

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 14.

TIME TO REACH PEAK PLASMA DILTIAZEM CONCENTRATIONS

SUBJECT No.	T _{max} (hrs.)	
	CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg
01	5.00	5.00
03	18.00	18.00
04	14.00	5.00
05	14.00	5.00
06	16.00	5.00
07	5.00	5.00
08	7.00	5.00
09	8.00	4.00
10	5.00	5.00
11	6.00	5.00
12	14.00	6.00
13	5.00	6.00
14	14.00	15.00
15	14.00	4.00
16	7.00	5.00
17	15.00	6.00
18	16.00	5.00
19	6.00	6.00
20	18.00	16.00
21	15.00	6.00
22	14.00	16.00
23	7.00	5.02
24	16.00	6.00
25	15.00	5.00
26	15.00	16.00
27	6.00	5.00
28	8.00	5.00
MEDIAN	14.00	5.00
MEAN	11.22	7.22
SD(±)	4.70	4.41
C.V.(%)	41.89	61.11
Range (Min.)	5.00	4.00
(Max.)	18.00	18.00
Num of subjects	27	27

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 15.

ANOVA ON DILTIAZEM T_{max}

The GLM Procedure

Dependent Variable: t_{max}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	1023.823414	36.565122	3.34	0.0016
Error	25	273.369451	10.934778		
Corrected Total	53	1297.192865			

R-Square	Coeff Var	Root MSE	t _{max} Mean
0.789261	35.85542	3.306778	9.222531

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	81.8295021	81.8295021	7.48	0.0113
subj(sq)	25	725.3965575	29.0158623	2.65	0.0089
peri	1	0.6640158	0.6640158	0.06	0.8074
drug	1	214.7516701	214.7516701	19.64	0.0002

The GLM Procedure
 Least Squares Means

drug	t _{max} LSMEAN	Standard Error	Pr > t
A	11.2637363	0.6368266	<.0001
B	7.2725733	0.6368266	<.0001

sq	t _{max} LSMEAN	Standard Error	Pr > t
AB	10.5000000	0.6485124	<.0001
BA	8.0363095	0.6249222	<.0001

peri	t _{max} LSMEAN	Standard Error	Pr > t
1	9.15718864	0.63682658	<.0001
2	9.37912088	0.63682658	<.0001

The GLM Procedure

Dependent Variable: t_{max}

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	81.82950213	81.82950213	2.82	0.1055

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	3.99116300	0.90060878	4.43	0.0002

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 16.

THE APPARENT HALF-LIFE OF DILTIAZEM

SUBJECT No.	T _{1/2} (hrs.)	
	CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg
01	8.49	5.81
03	8.08	8.41
04	10.15	8.47
05	7.24	6.58
06	14.06	7.43
07	7.70	7.37
08	7.23	6.69
09	6.27	6.27
10	6.47	6.38
11	7.99	9.04
12	6.32	6.88
13	8.55	5.74
14	8.37	8.10
15	8.35	8.69
16	6.82	7.09
17	7.88	7.60
18	6.80	6.60
19	11.61	10.17
20	6.83	6.99
21	7.05	8.65
22	8.07	7.83
23	8.26	8.90
24	9.92	9.39
25	6.07	6.50
26	6.33	6.16
27	6.71	9.78
28	11.47	7.42
MEAN	8.11	7.59
SD (±)	1.90	1.24
C.V. (%)	23.37	16.29
Range (Min.)	6.07	5.74
(Max.)	14.06	10.17
Num of subjects	27	27

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 17.

ANOVA ON DILTIAZEM HALF-LIFE

The GLM Procedure

Dependent Variable: t_{half}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	95.7225902	3.4186639	2.08	0.0343
Error	25	41.1546597	1.6461864		
Corrected Total	53	136.8772499			

R-Square	Coeff Var	Root MSE	t_{half} Mean
0.699332	16.33970	1.283038	7.852274

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	5.43115786	5.43115786	3.30	0.0813
subj (sq)	25	83.41875997	3.33675040	2.03	0.0417
peri	1	3.18006106	3.18006106	1.93	0.1768
drug	1	3.43824781	3.43824781	2.09	0.1608

The GLM Procedure
 Least Squares Means

drug	t_{half} LSMEAN	Standard Error	Pr > t
A	8.09302481	0.24709030	<.0001
B	7.58801505	0.24709030	<.0001

sq	t_{half} LSMEAN	Standard Error	Pr > t
AB	7.52316342	0.25162444	<.0001
BA	8.15787644	0.24247138	<.0001

peri	t_{half} LSMEAN	Standard Error	Pr > t
1	7.59768066	0.24709030	<.0001
2	8.08335920	0.24709030	<.0001

The GLM Procedure

Dependent Variable: t_{half}

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	5.43115786	5.43115786	1.63	0.2138

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	0.50500977	0.34943845	1.45	0.1608

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 18.

THE ELIMINATION RATE CONSTANT OF DILTIAZEM

SUBJECT No.	K_{e1} (hour ⁻¹)	
	CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg
01	0.082	0.119
03	0.086	0.082
04	0.068	0.082
05	0.096	0.105
06	0.049	0.093
07	0.090	0.094
08	0.096	0.104
09	0.111	0.111
10	0.107	0.109
11	0.087	0.077
12	0.110	0.101
13	0.081	0.121
14	0.083	0.086
15	0.083	0.080
16	0.102	0.098
17	0.088	0.091
18	0.102	0.105
19	0.060	0.068
20	0.101	0.099
21	0.098	0.080
22	0.086	0.089
23	0.084	0.078
24	0.070	0.074
25	0.114	0.107
26	0.110	0.112
27	0.103	0.071
28	0.060	0.093
MEAN	0.089	0.094
SD (±)	0.017	0.015
C.V. (%)	18.985	15.872
Range (Min.)	0.049	0.068
(Max.)	0.114	0.121
Num of subjects	27	27

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 19.

ANOVA ON DILTIAZEM k_{e1}

The GLM Procedure

Dependent Variable: k_{e1}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	0.00978436	0.00034944	2.38	0.0158
Error	25	0.00367189	0.00014688		
Corrected Total	53	0.01345625			

R-Square	Coeff Var	Root MSE	k_{e1} Mean
0.727124	13.26445	0.012119	0.091366

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.00021298	0.00021298	1.45	0.2398
subj(sq)	25	0.00914047	0.00036562	2.49	0.0132
peri	1	0.00015737	0.00015737	1.07	0.3105
drug	1	0.00025803	0.00025803	1.76	0.1970

The GLM Procedure
Least Squares Means

drug	k_{e1} LSMEAN	Standard Error	Pr > t
A	0.08925239	0.00233395	<.0001
B	0.09362724	0.00233395	<.0001

sq	k_{e1} LSMEAN	Standard Error	Pr > t
AB	0.09342713	0.00237678	<.0001
BA	0.08945250	0.00229032	<.0001

peri	k_{e1} LSMEAN	Standard Error	Pr > t
1	0.09314813	0.00233395	<.0001
2	0.08973151	0.00233395	<.0001

The GLM Procedure

Dependent Variable: k_{e1}

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.00021298	0.00021298	0.58	0.4525

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST -- REF	-0.00437485	0.00330070	-1.33	0.1970

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 1. 20.

THE CORRELATION COEFFICIENT (r value) OF THE MOST LINEAR PORTION
 OF THE TERMINAL ELIMINATION PHASE FOR PLASMA DILTIAZEM

SUBJECT No.	CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg
01	0.99873	0.98757
03	0.97915	0.99185
04	0.99971	0.99689
05	0.99957	0.99766
06	0.99763	0.99975
07	0.99995	0.99920
08	0.98495	0.99923
09	0.99768	0.99976
10	0.99918	0.99842
11	0.99728	0.99507
12	0.98745	0.99501
13	0.97799	0.99817
14	0.99906	0.99917
15	0.99885	0.99728
16	0.99895	0.99720
17	0.99481	0.99723
18	0.99994	0.99804
19	0.96072	0.99026
20	0.99823	0.99820
21	0.99705	0.99662
22	0.99596	0.99728
23	0.99965	0.99936
24	0.99937	0.99467
25	0.99987	1.00000
26	0.99789	0.99945
27	0.99412	0.99791
28	0.99702	0.99959
MEAN	0.99447	0.99707
SD(±)	0.00909	0.00303
C.V. (%)	0.91422	0.30370
Range (Min.)	0.96072	0.98757
(Max.)	0.99995	1.00000
Num of subjects	27	27

N.C. = No Calculation of Kel

FIGURES

MEAN PLASMA DILTIAZEM CONCENTRATIONS

STUDY # 2443 (N=27)

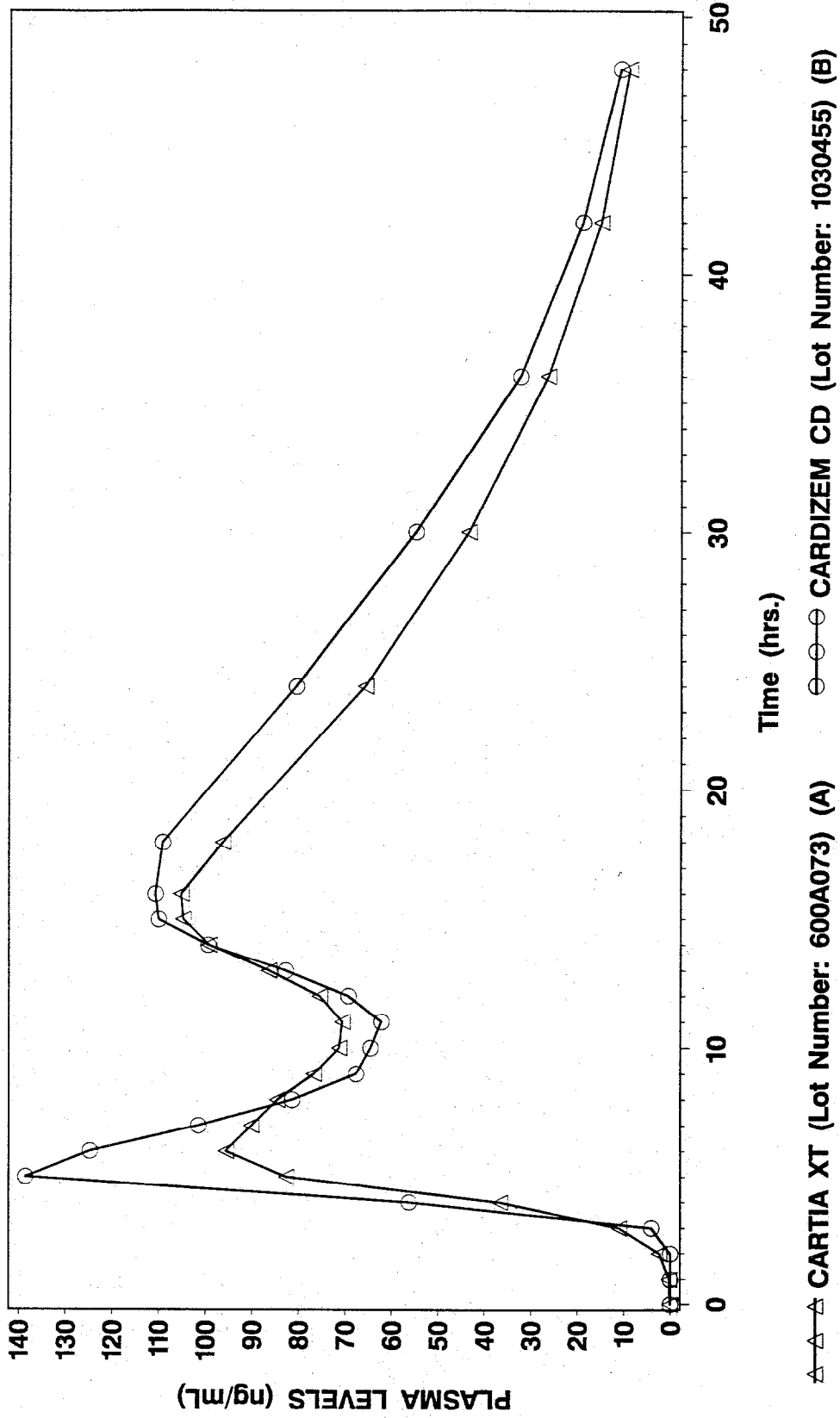


FIGURE 1.1

SEMI LOG MEAN PLASMA DILTIAZEM CONCENTRATIONS

STUDY # 2443 (N=27)

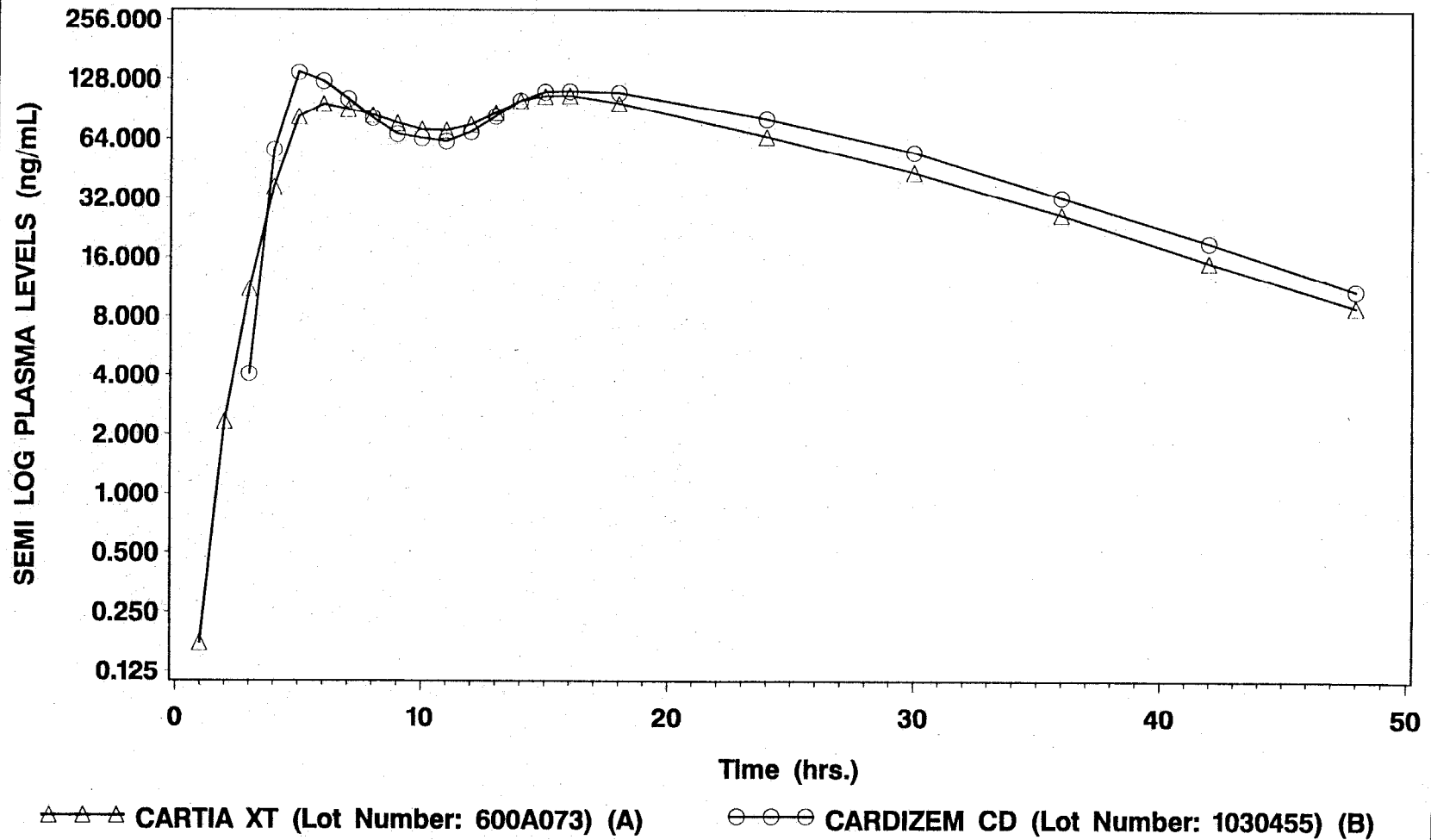


FIGURE 1.2

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 01

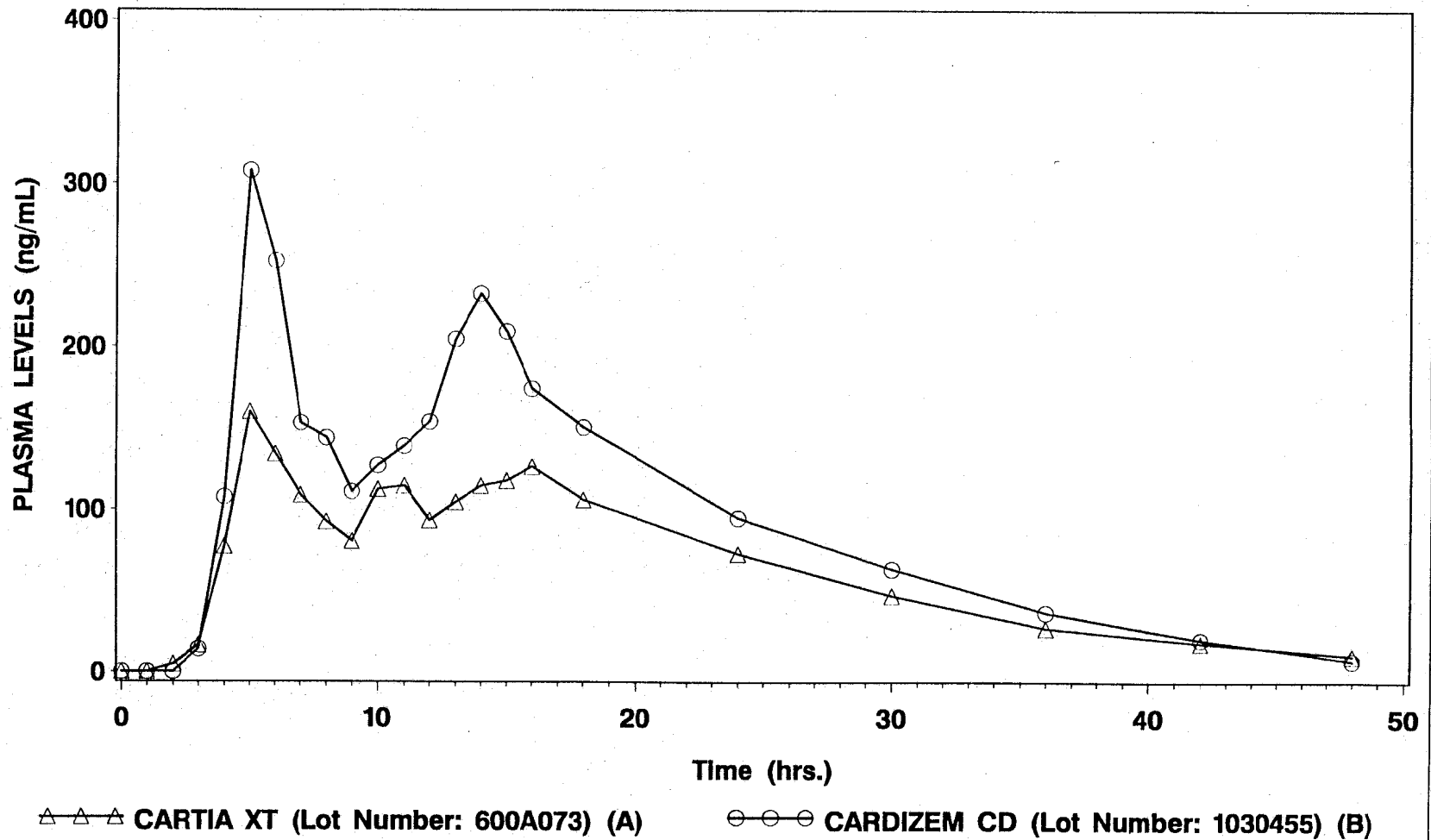


FIGURE 1.3

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 03

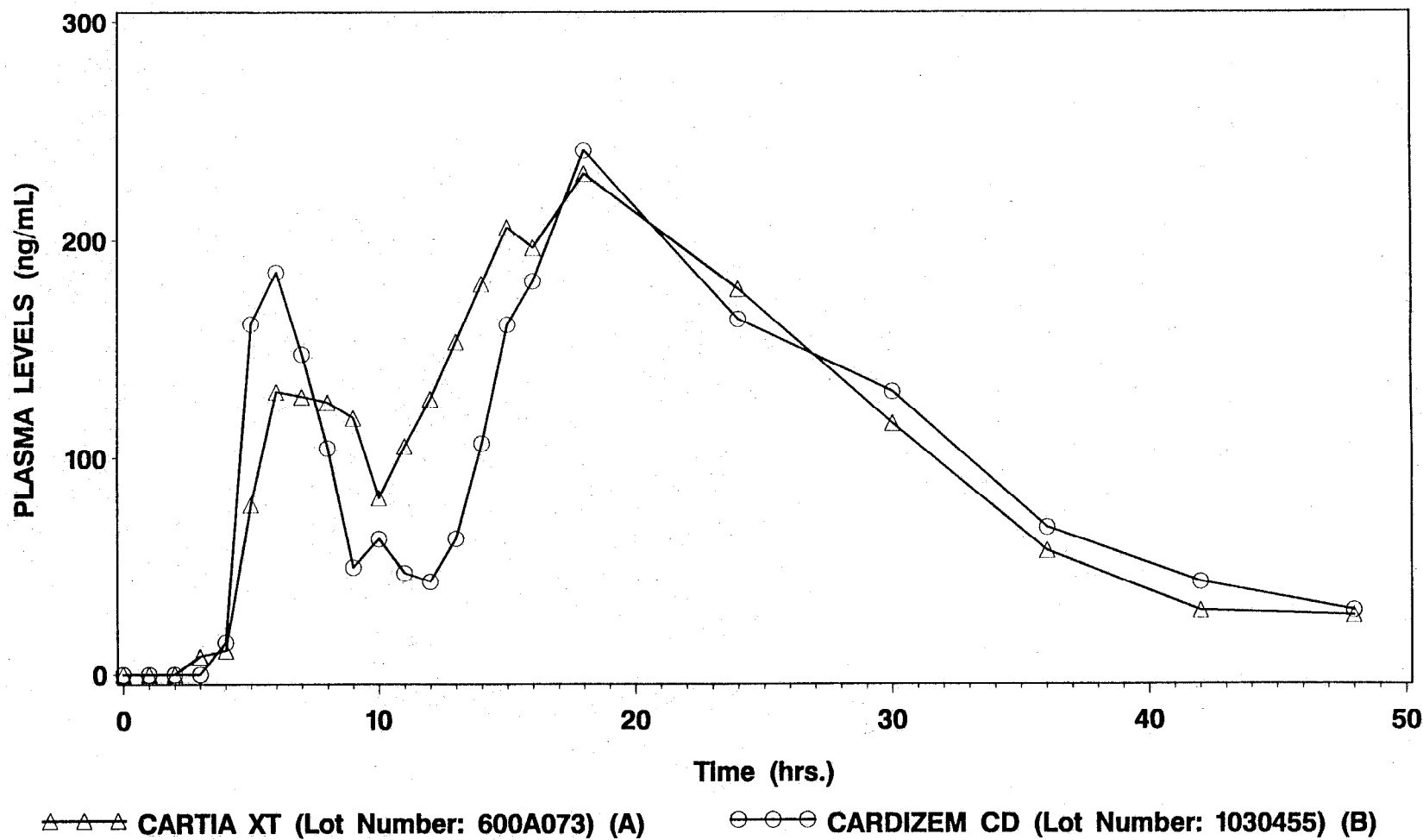


FIGURE 1.4

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 04

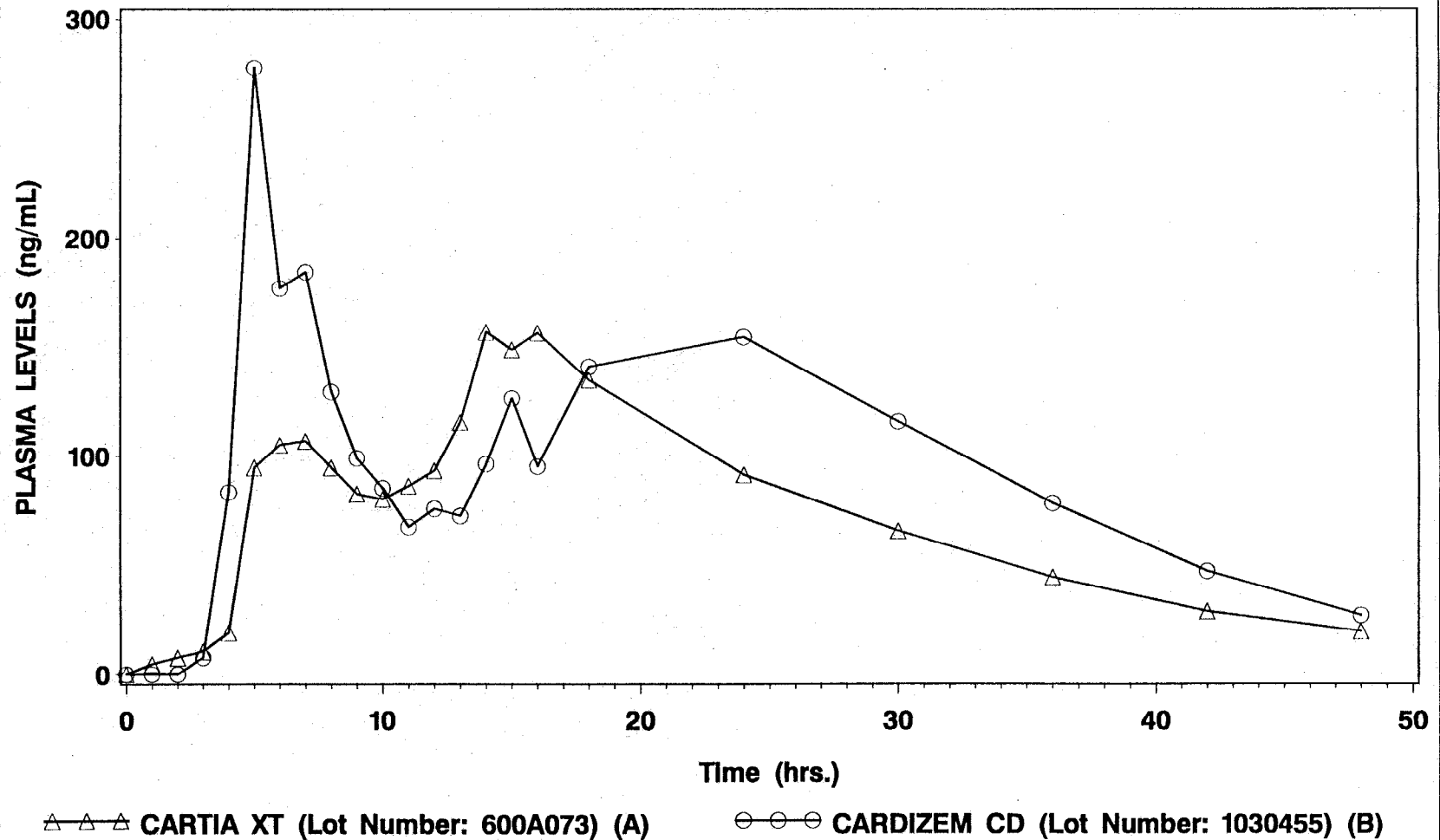


FIGURE 1.5

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 05

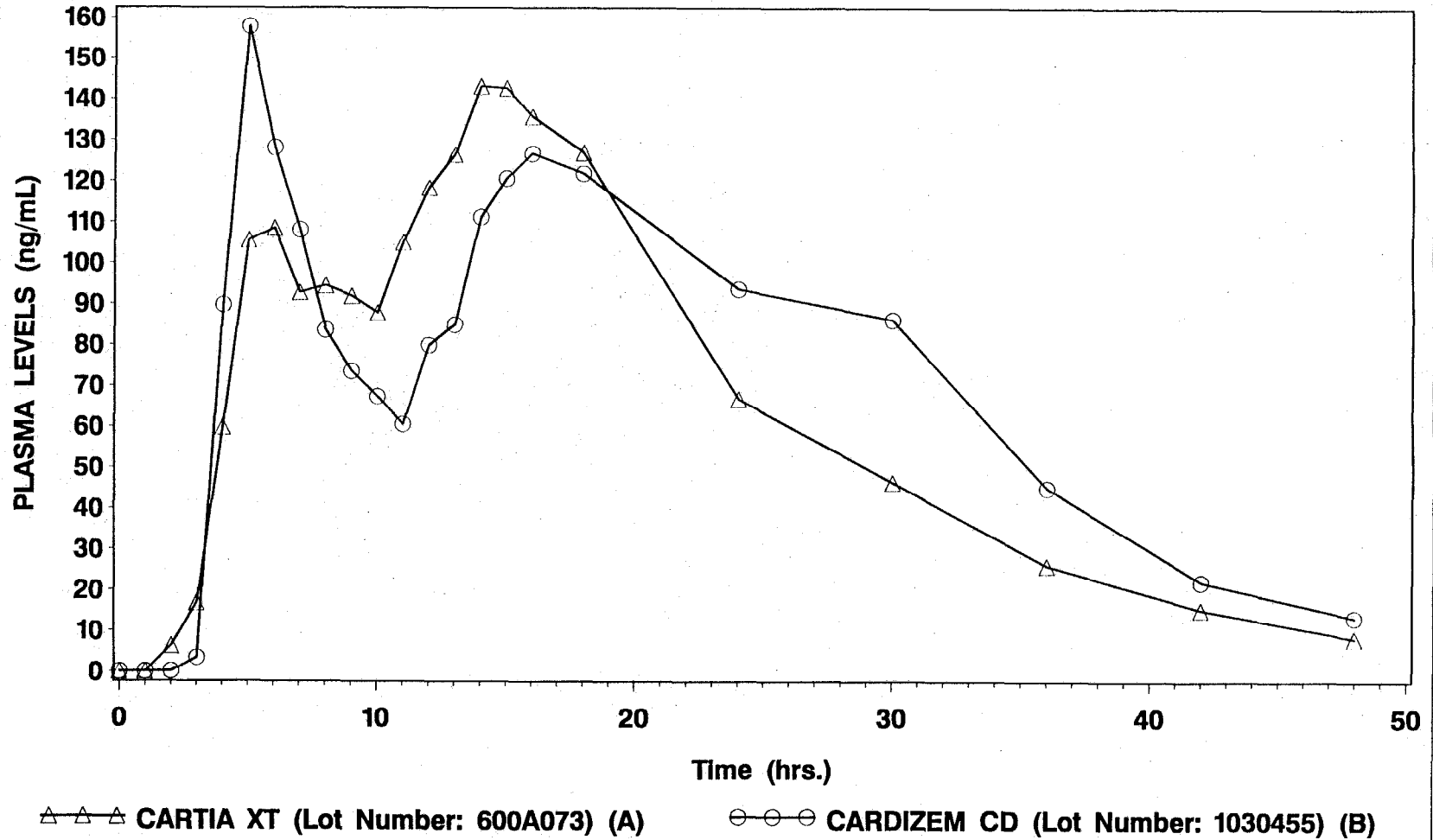


FIGURE 1.6

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 06

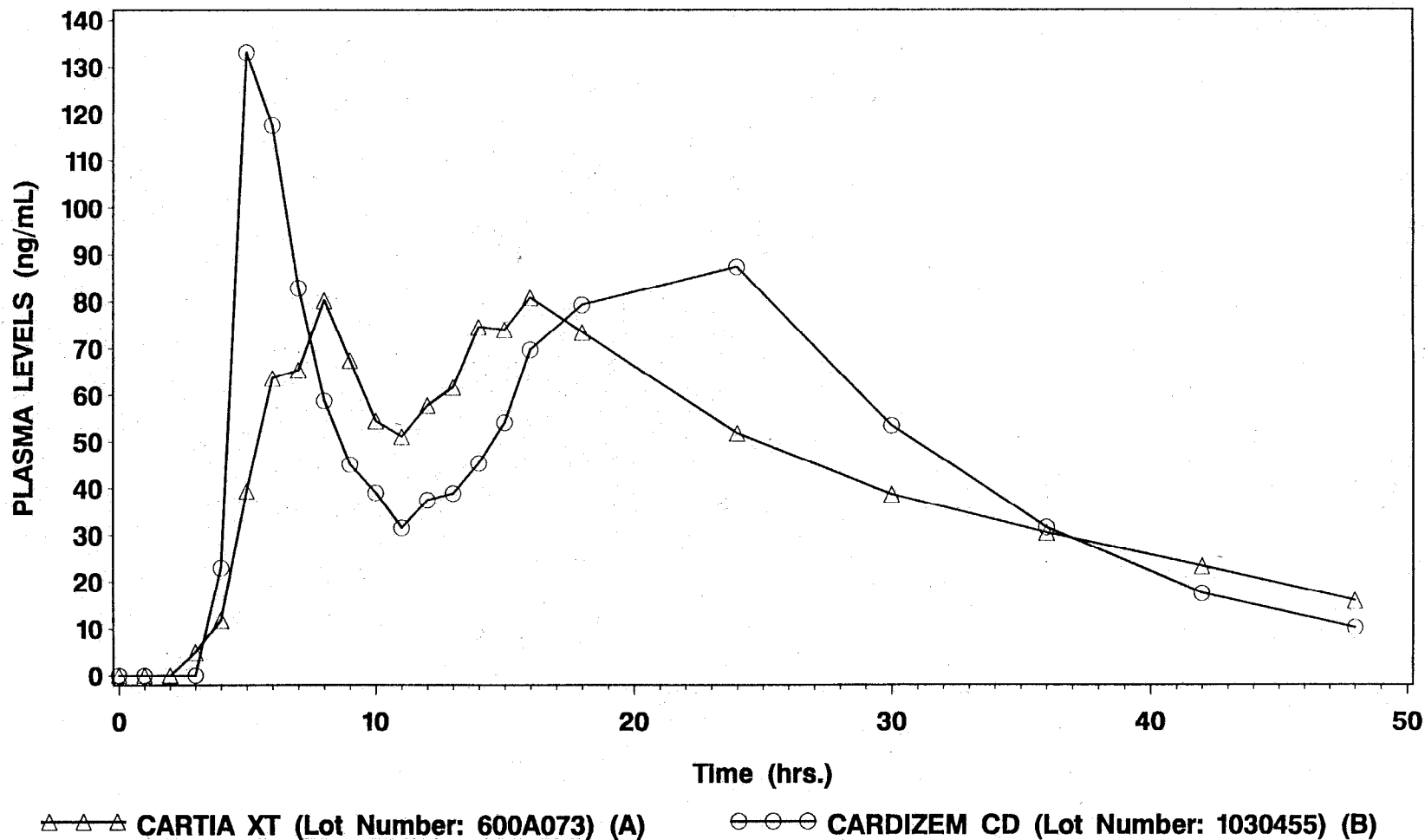


FIGURE 1.7

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 07

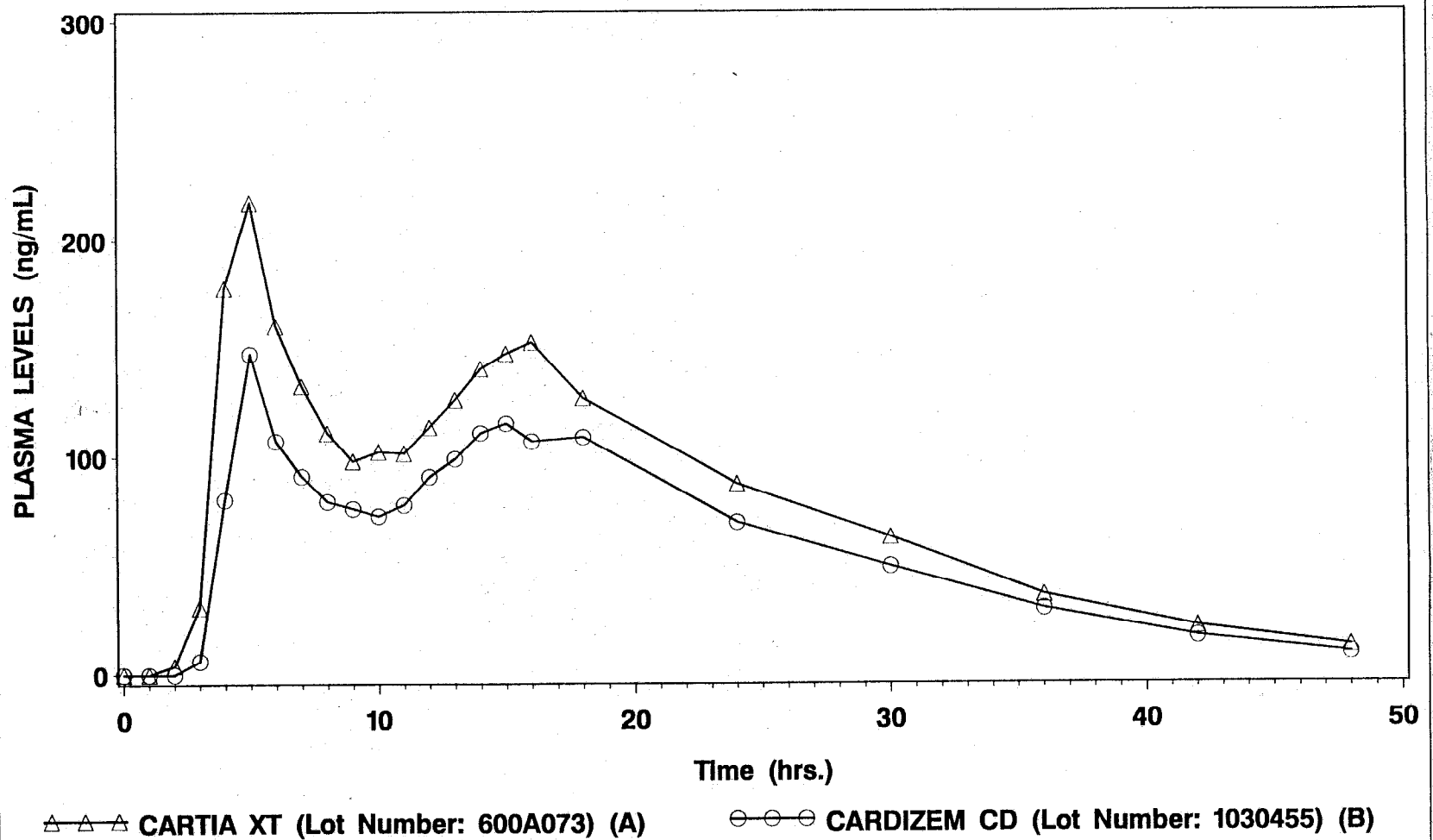


FIGURE 1.8

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 08

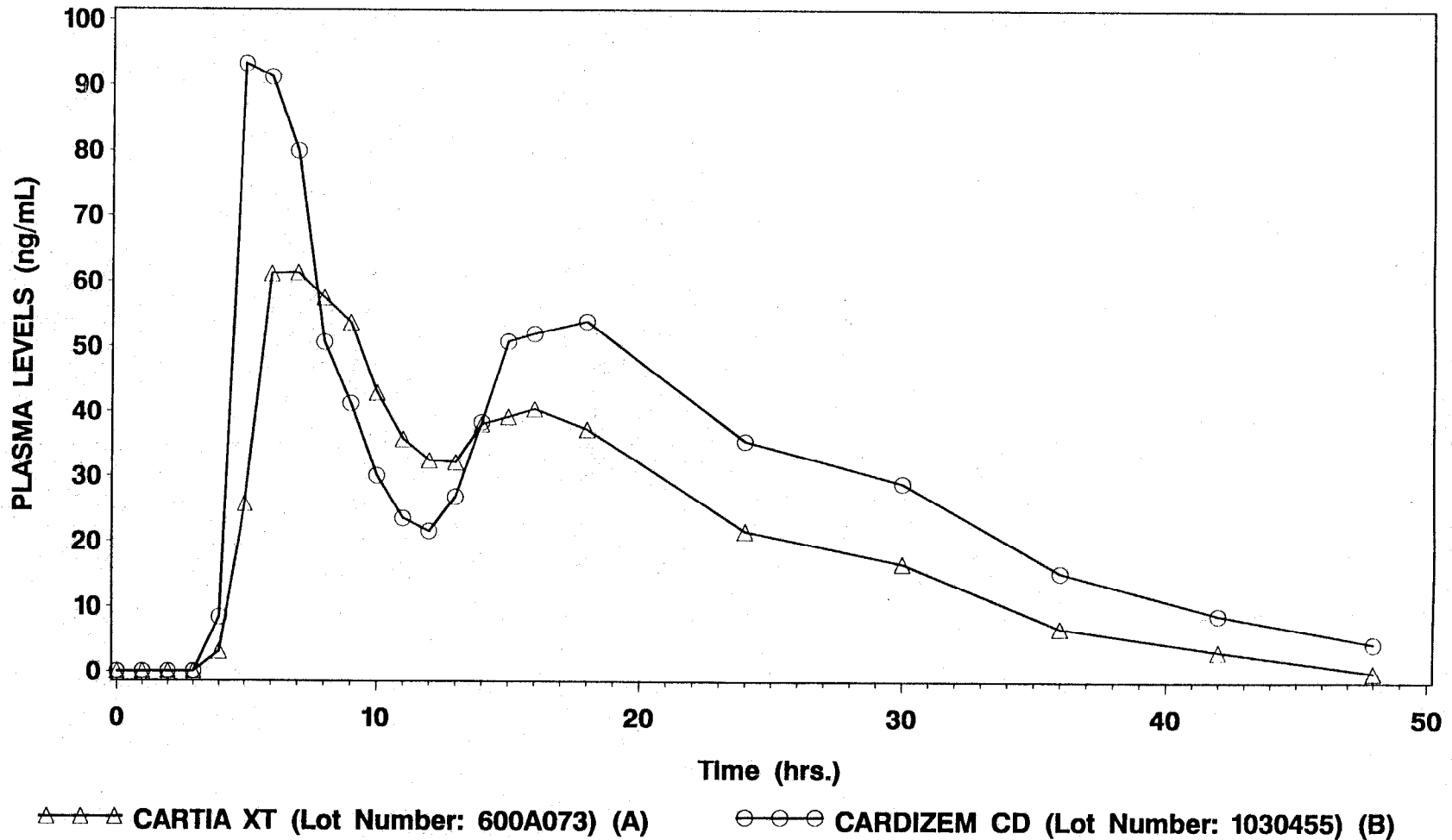


FIGURE 1.9

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 09

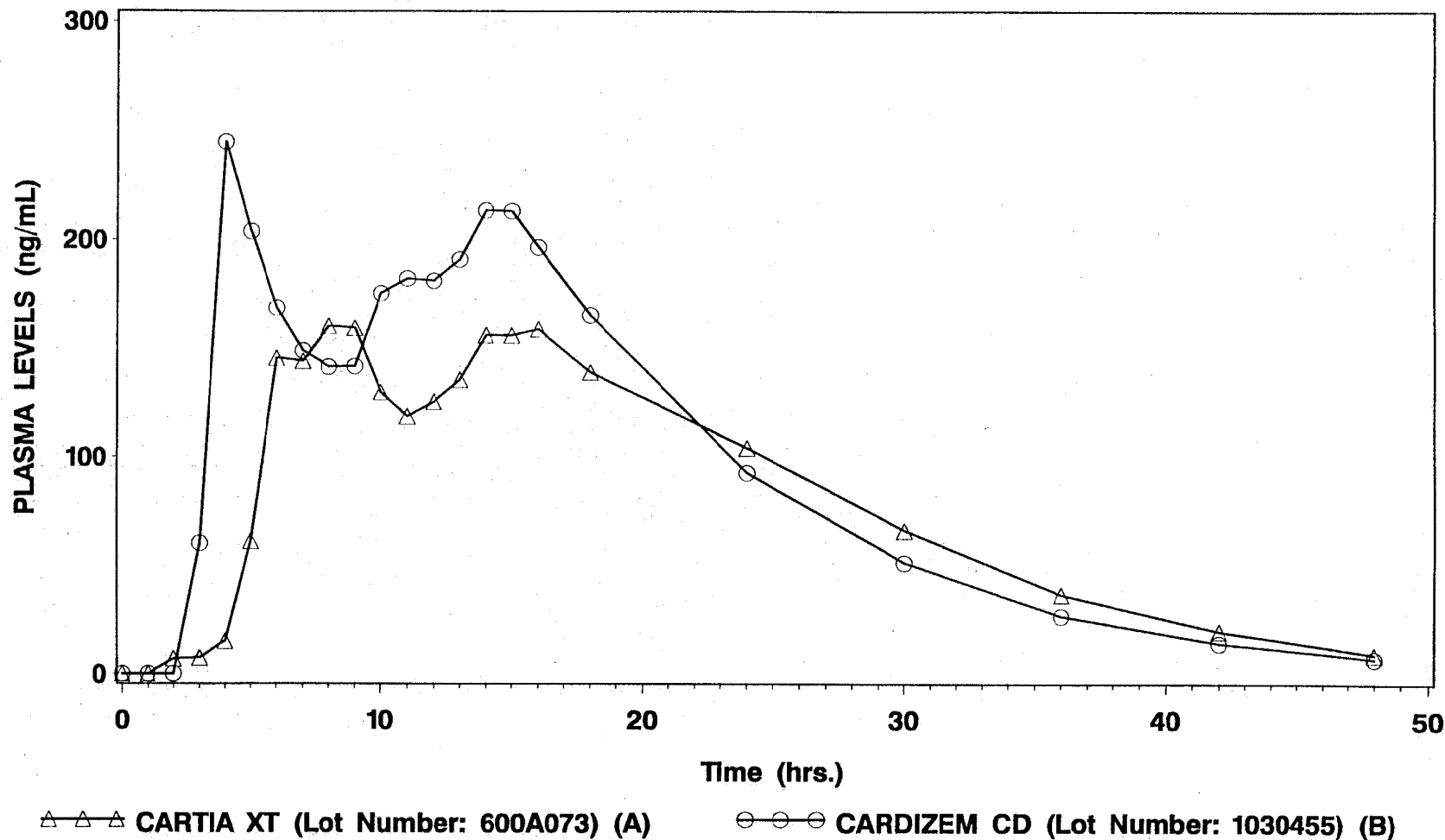


FIGURE 1.10

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 10

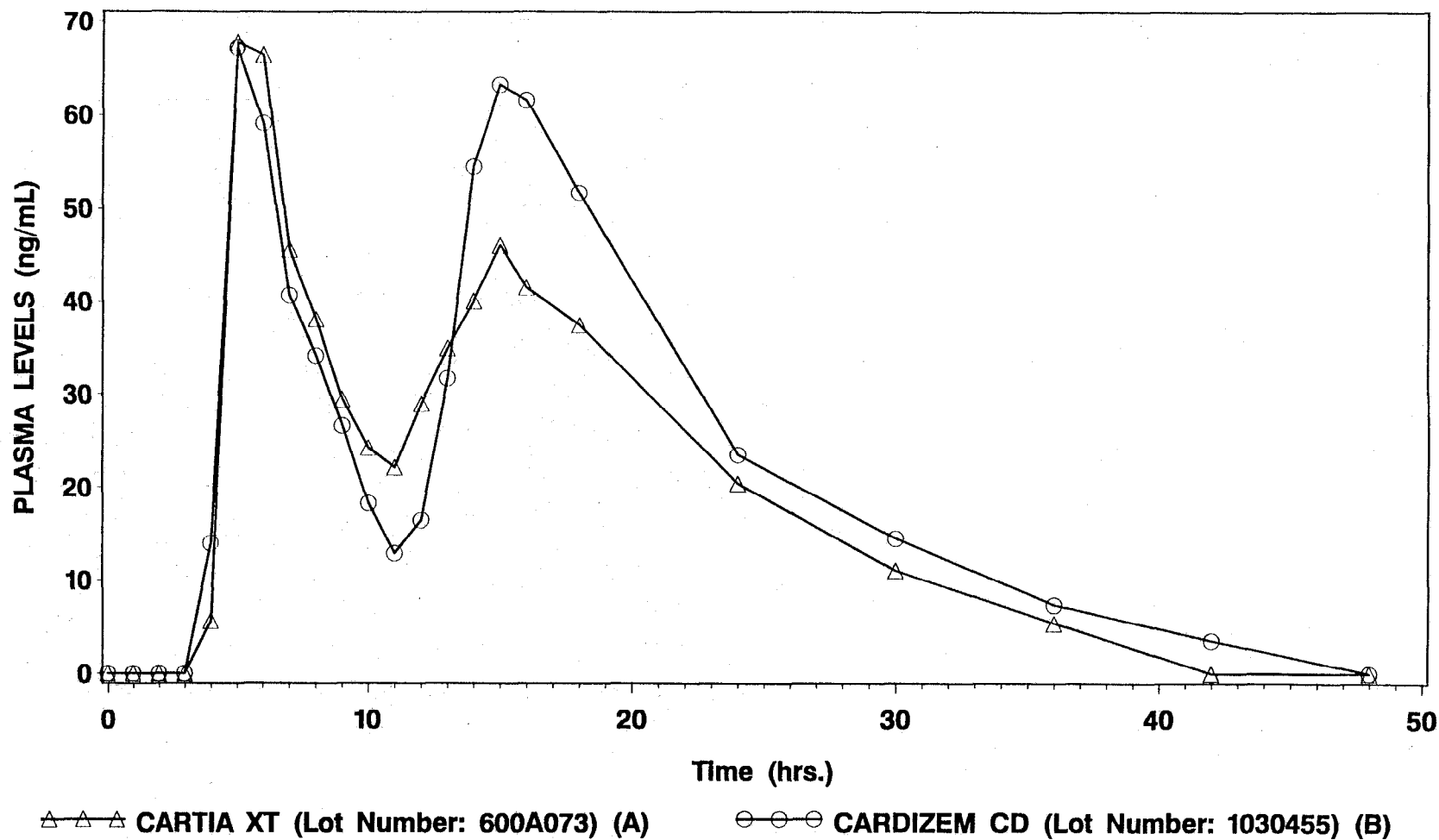


FIGURE 1.11

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 11

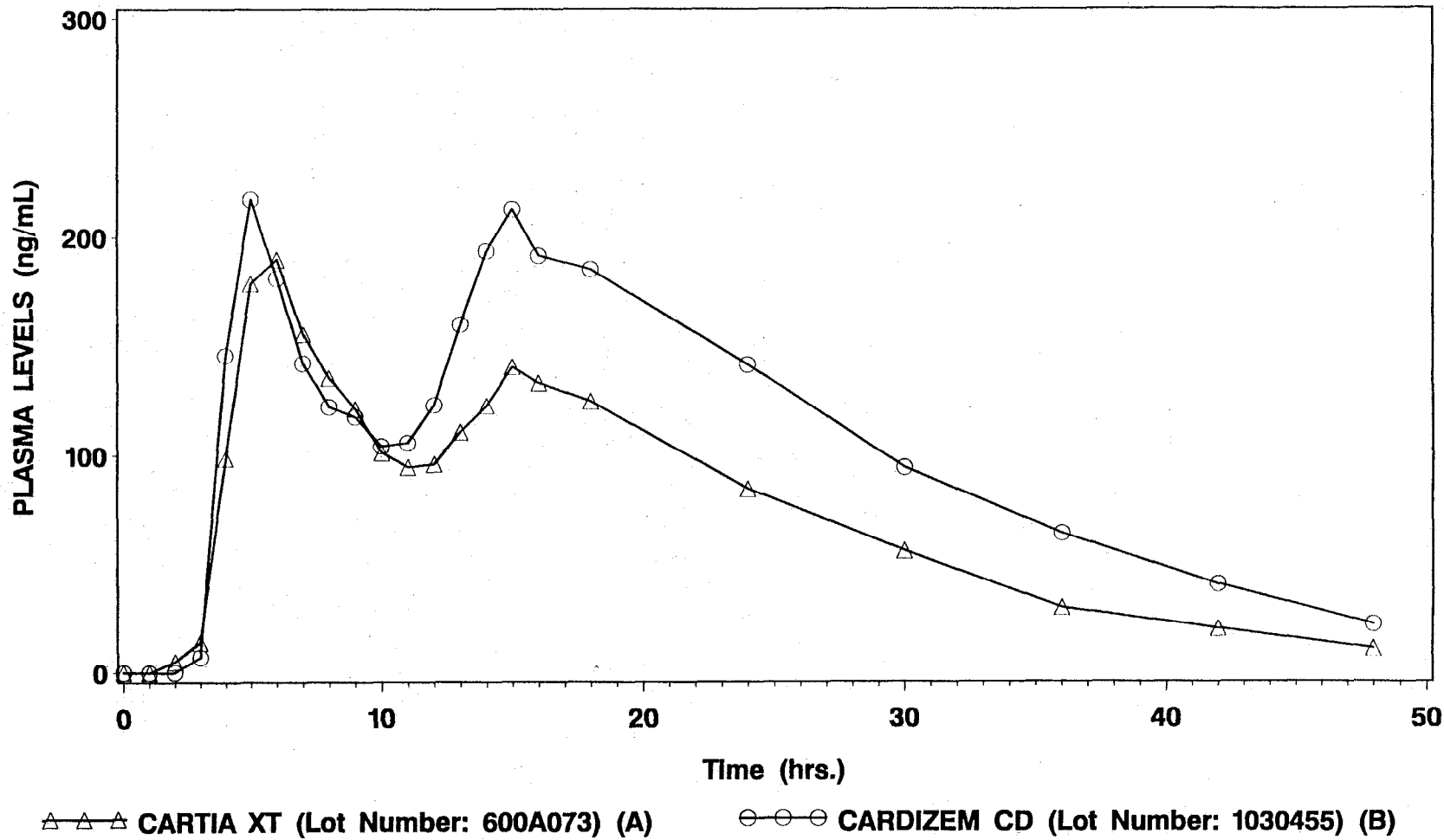


FIGURE 1.12

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 12

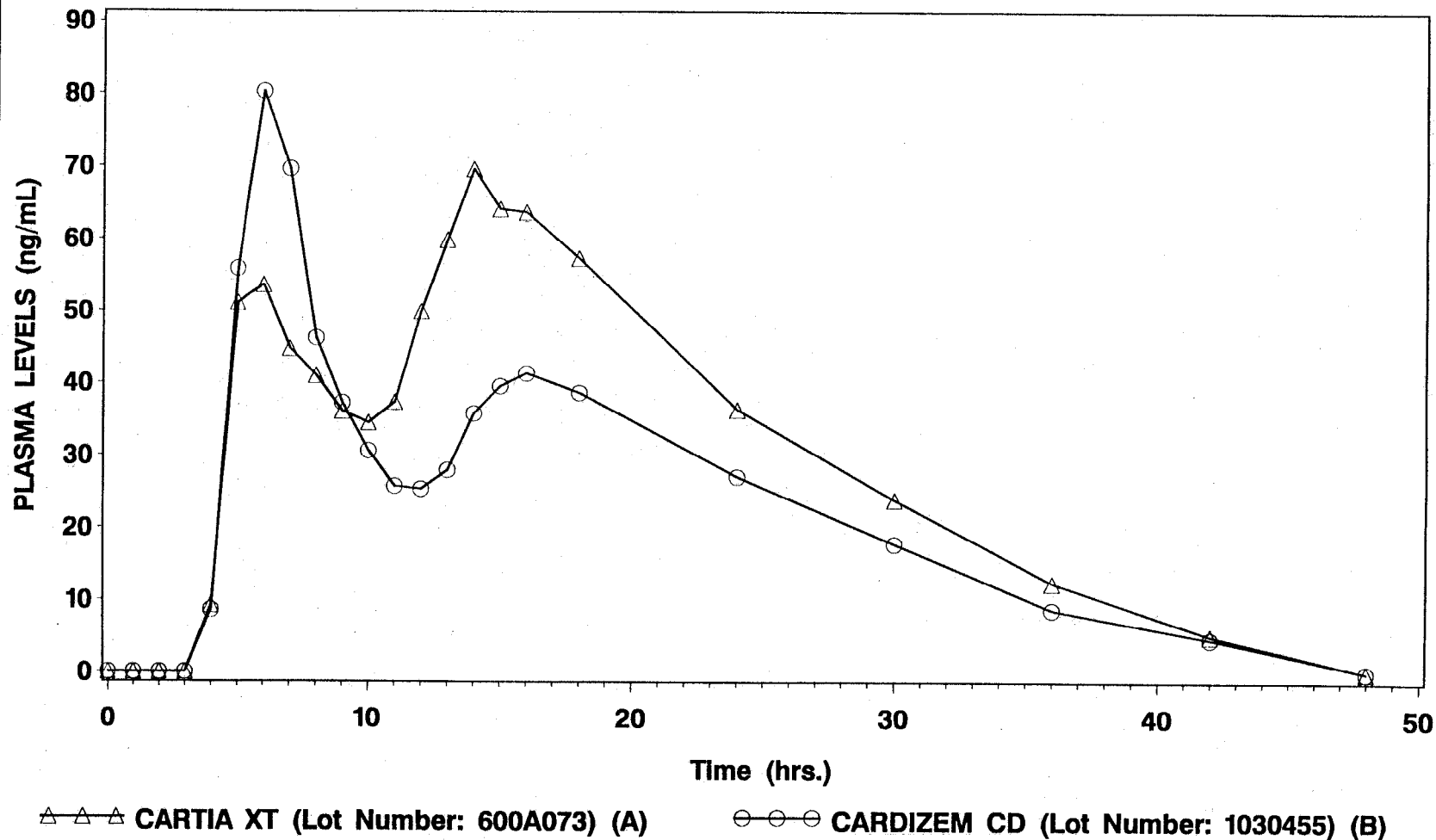


FIGURE 1.13

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 13

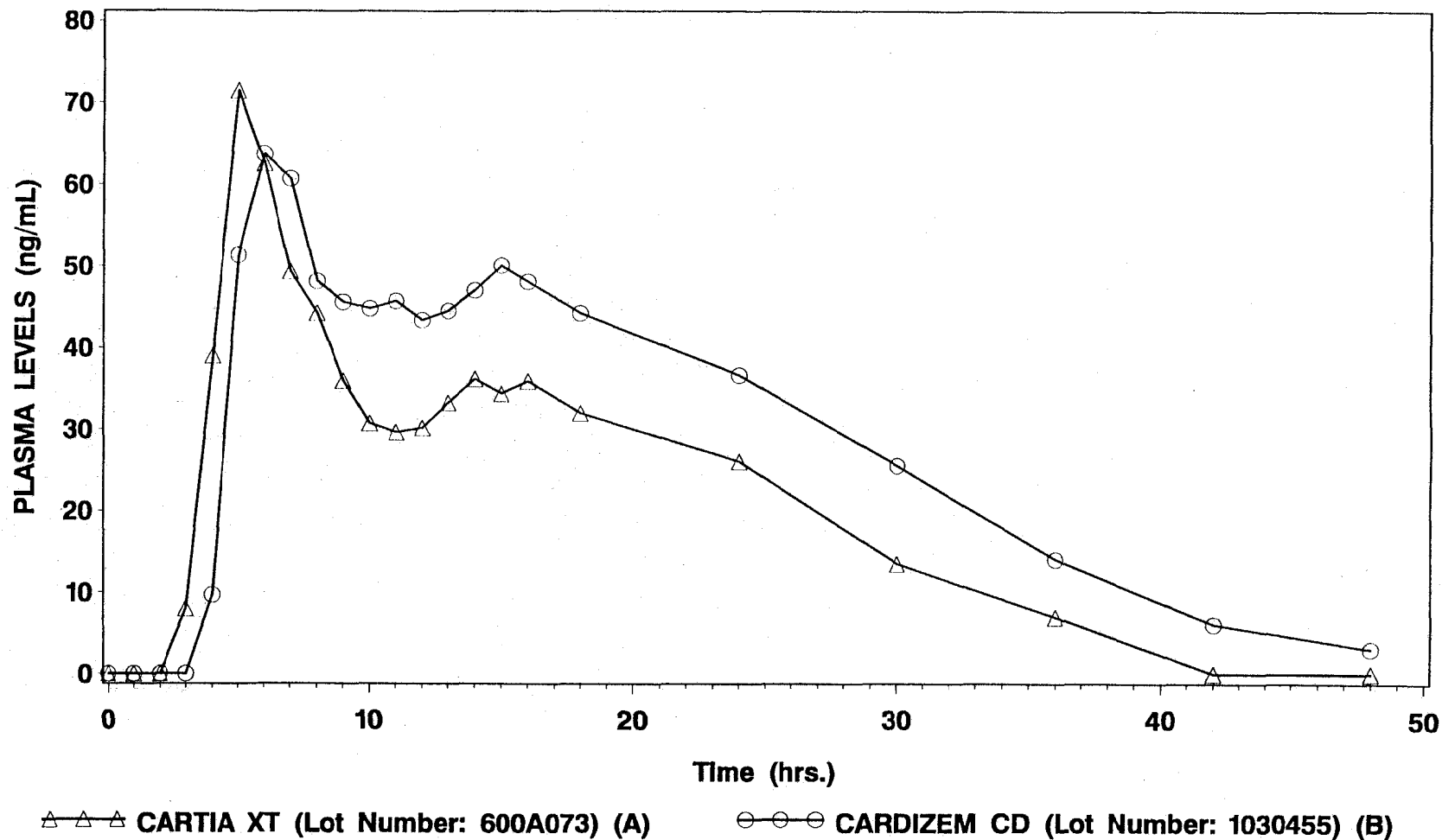


FIGURE 1.14

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 14

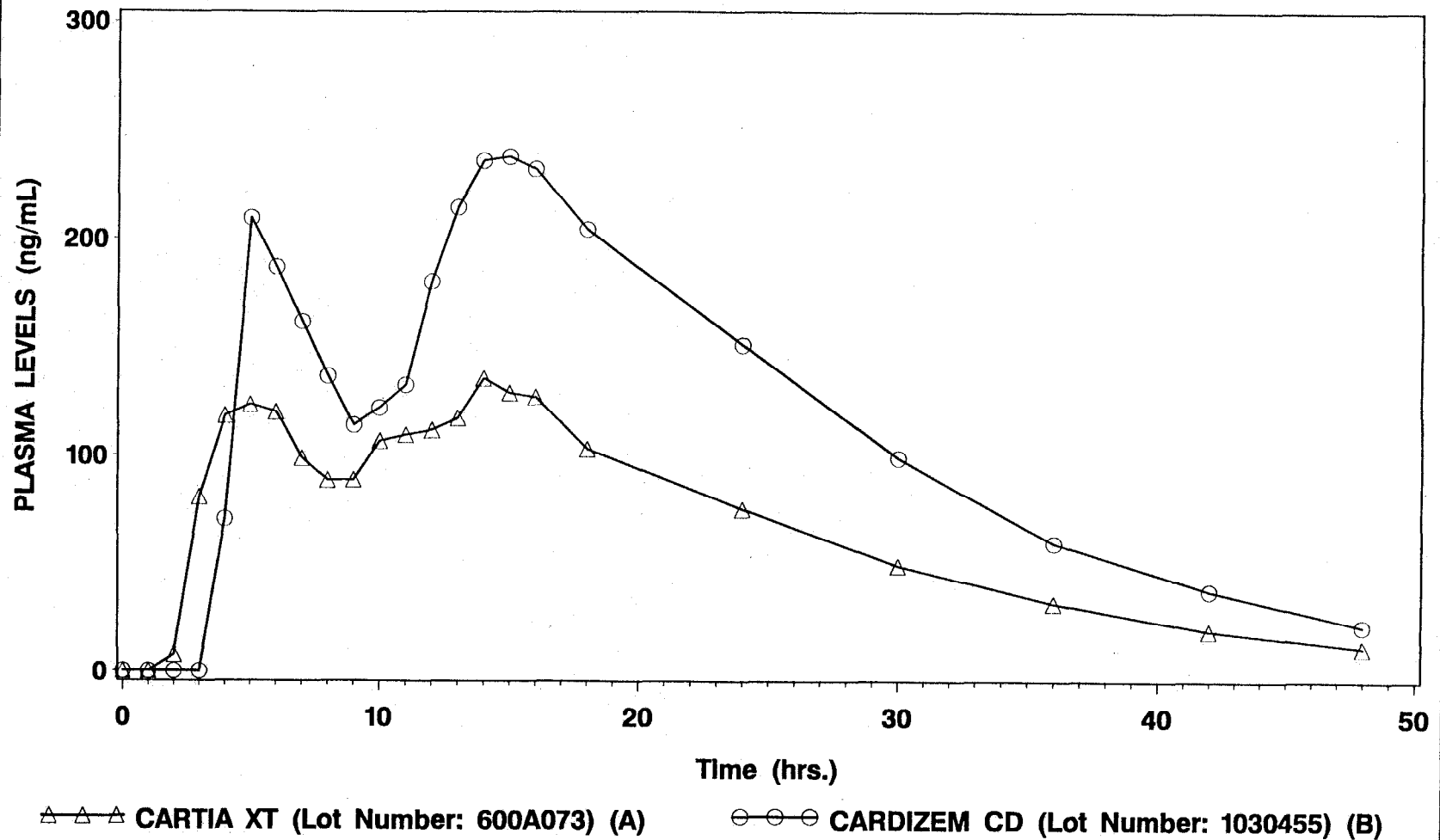


FIGURE 1.15

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 15

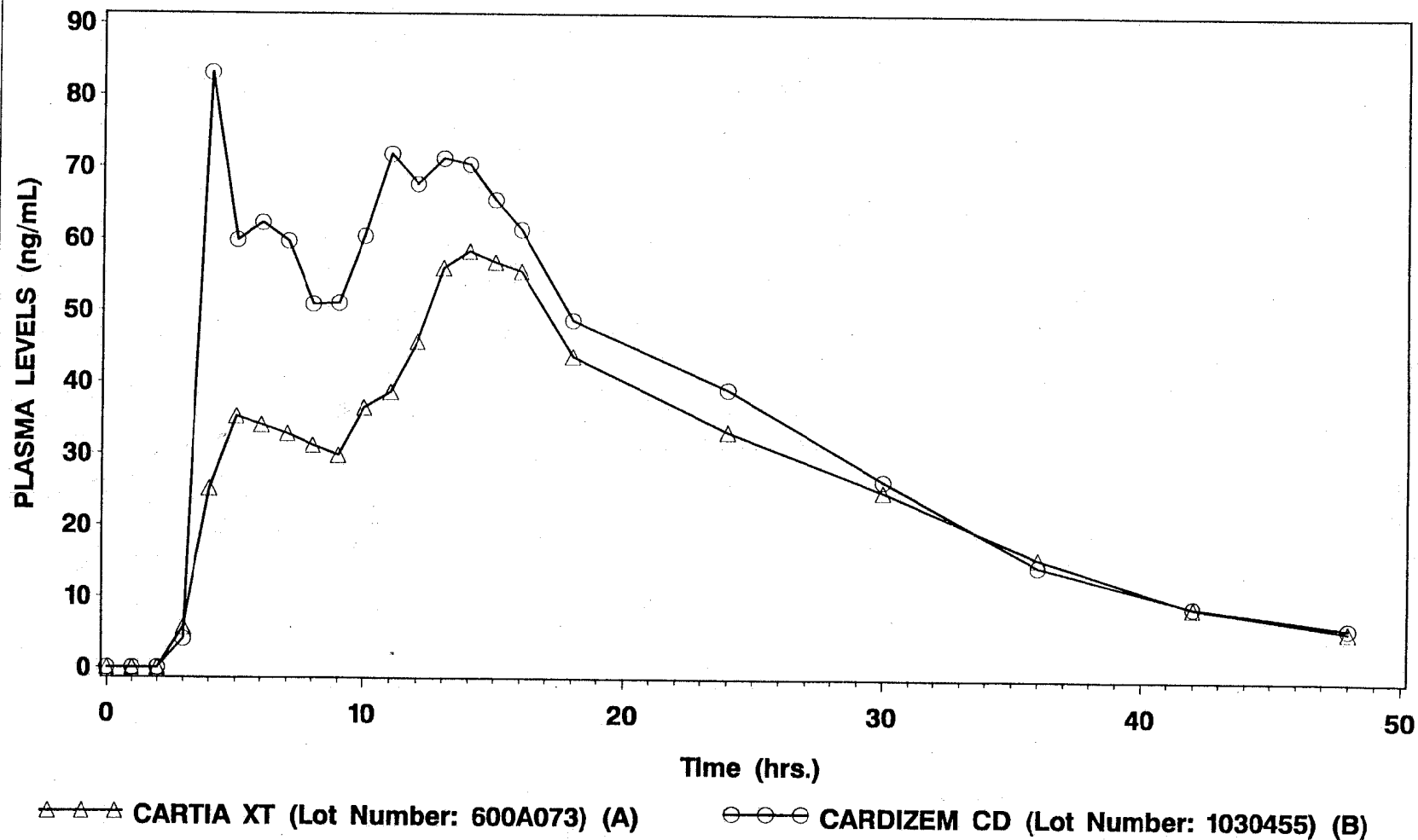


FIGURE 1.16

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 16

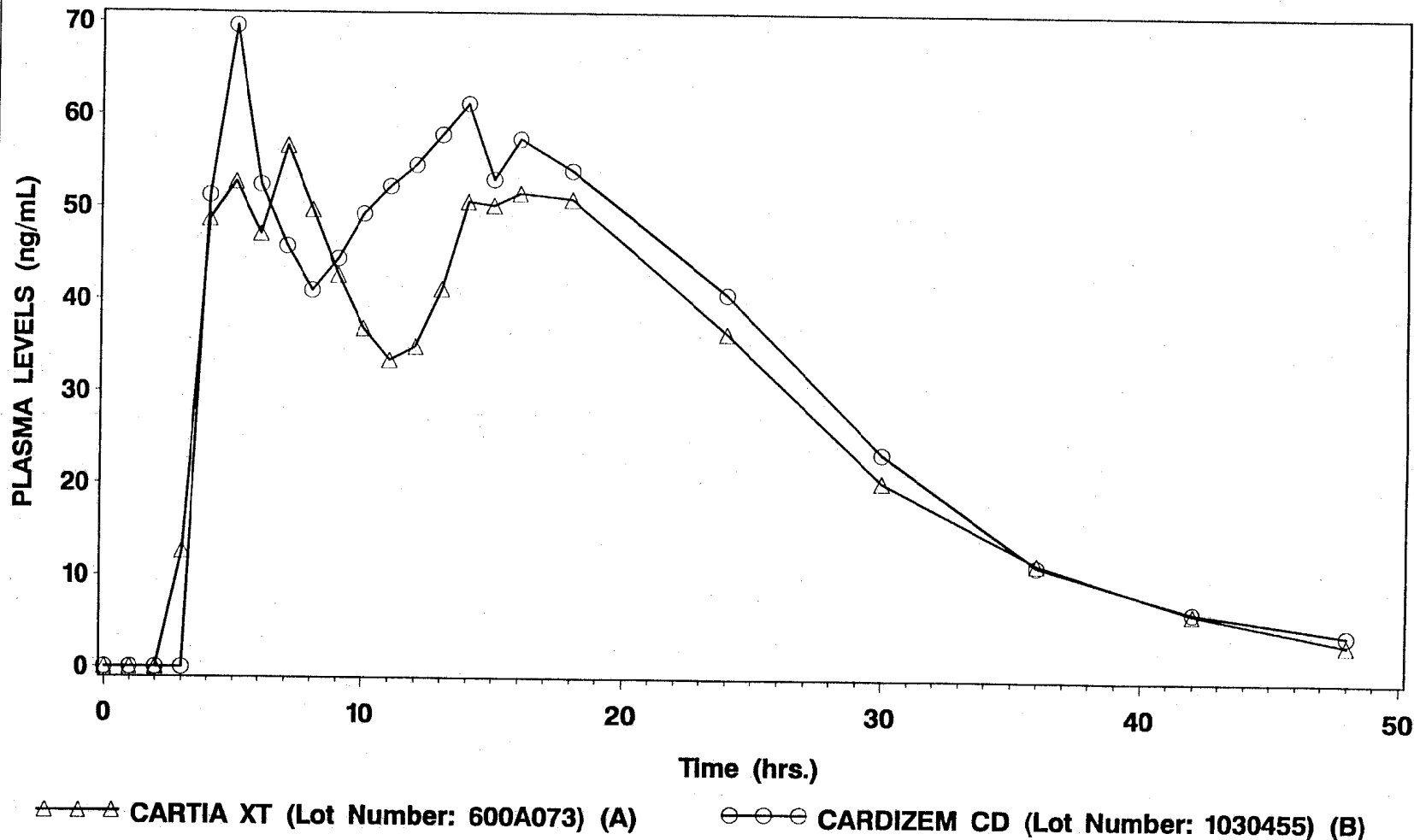


FIGURE 1.17

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 17

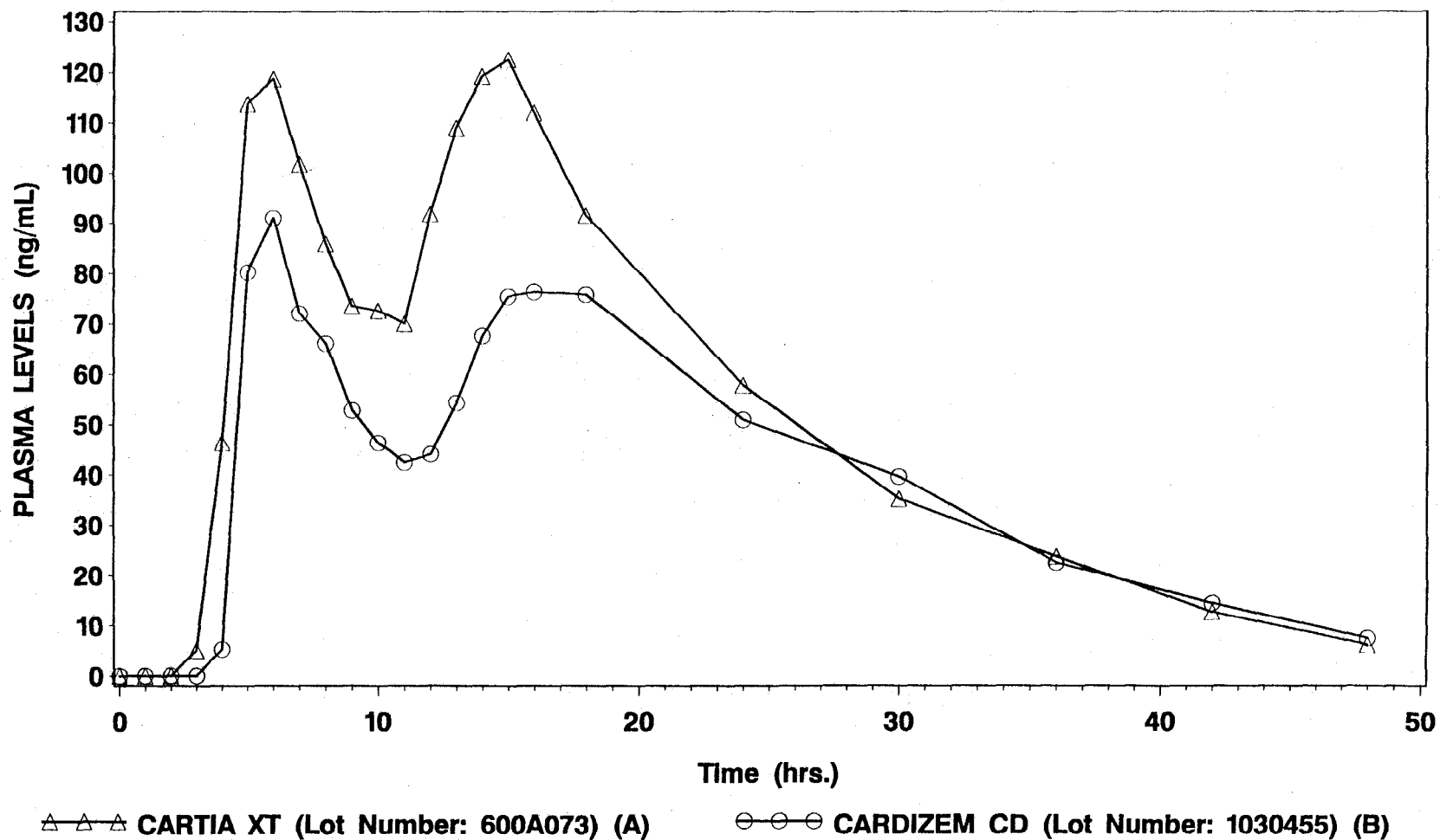


FIGURE 1.18

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 18

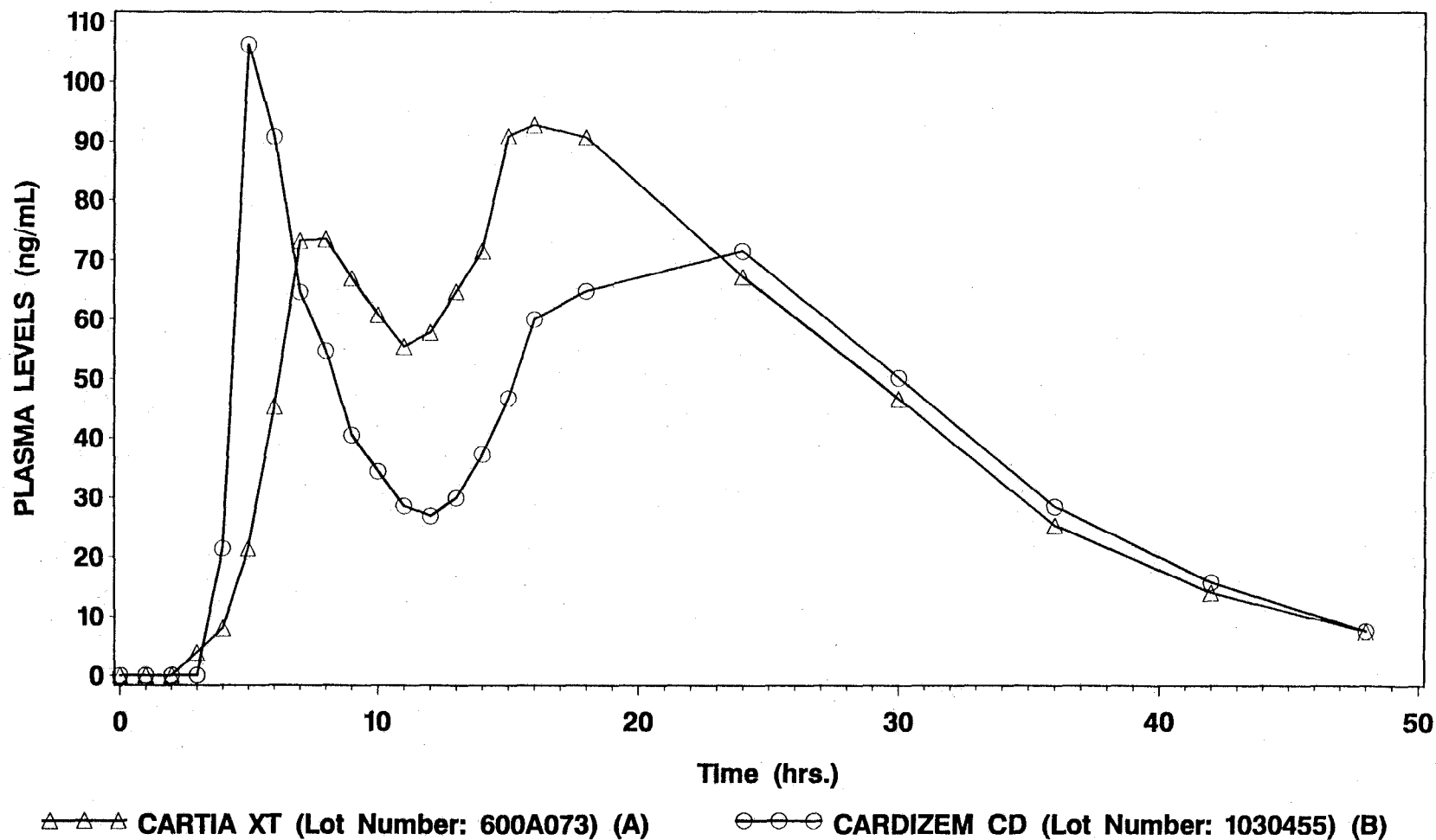


FIGURE 1.19

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 19

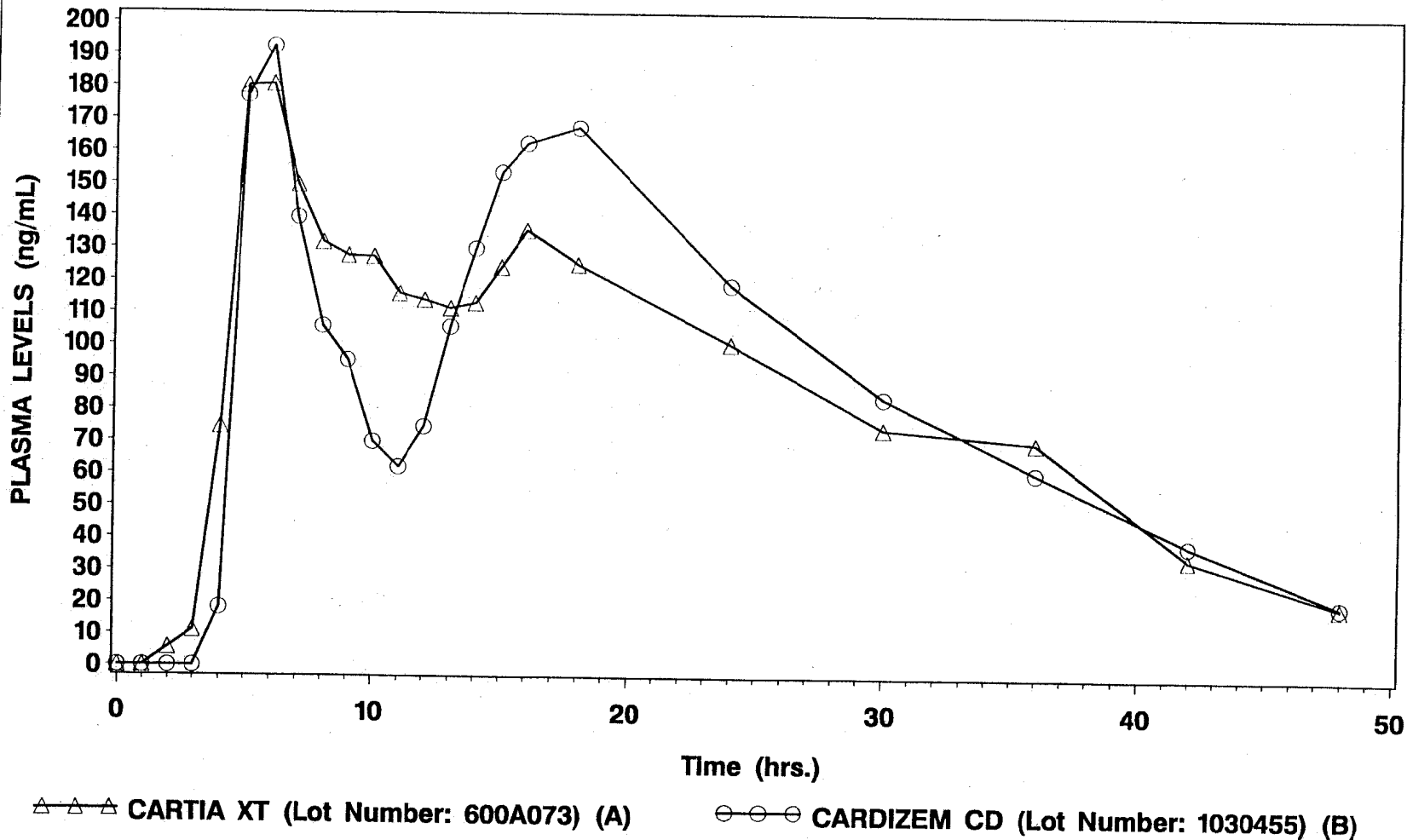


FIGURE 1.20

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 20

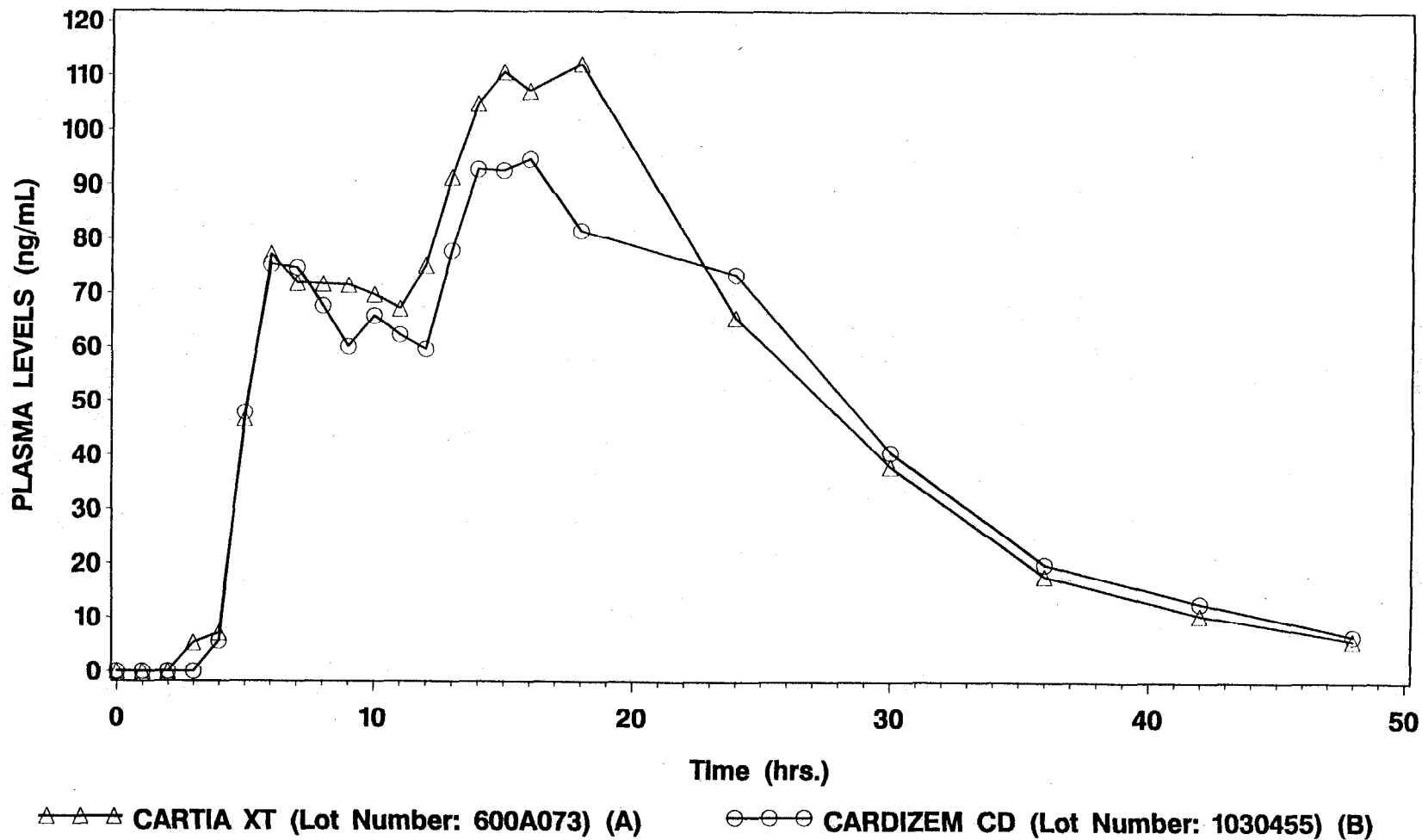


FIGURE 1.21

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 21

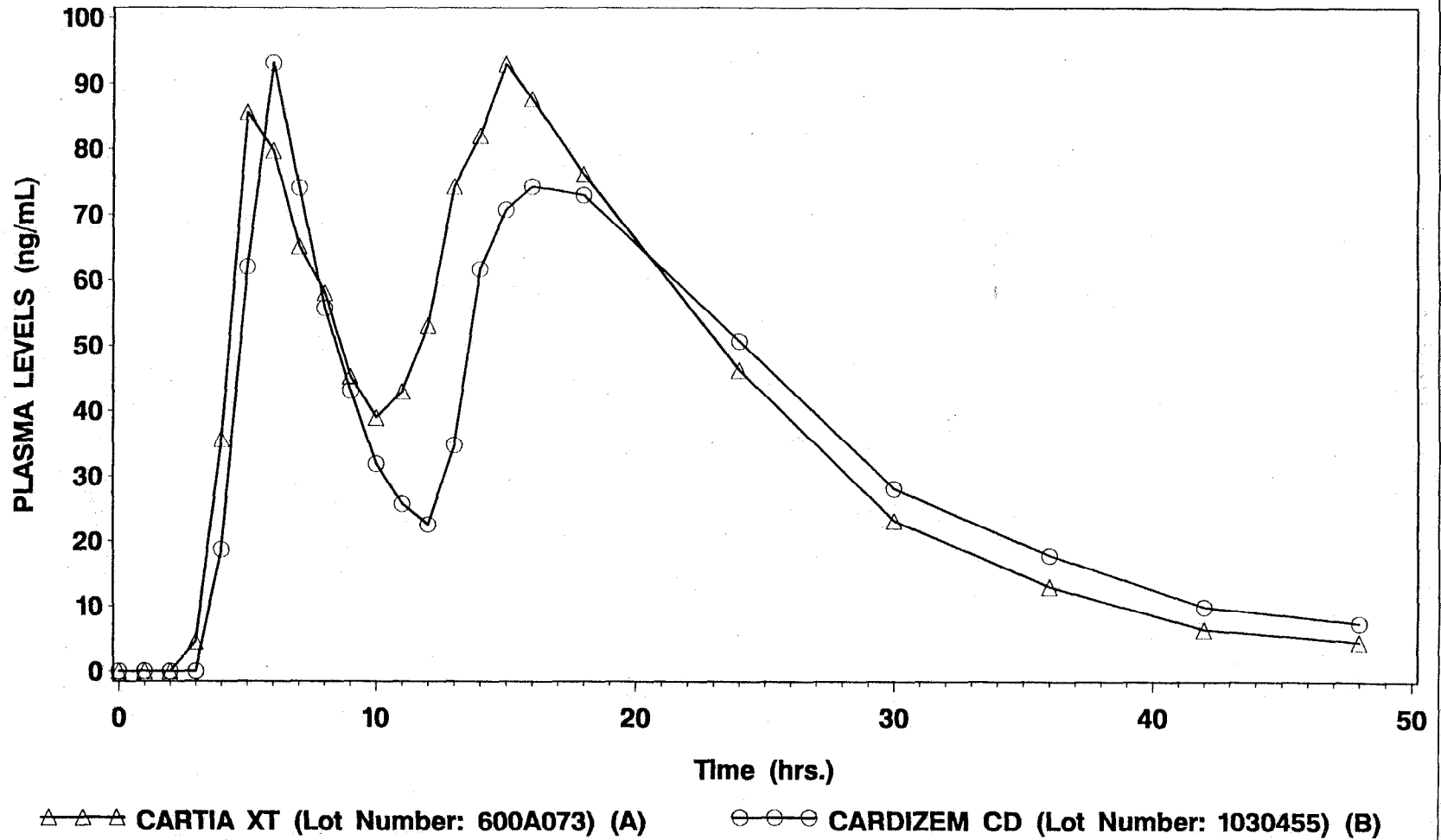


FIGURE 1.22

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 22

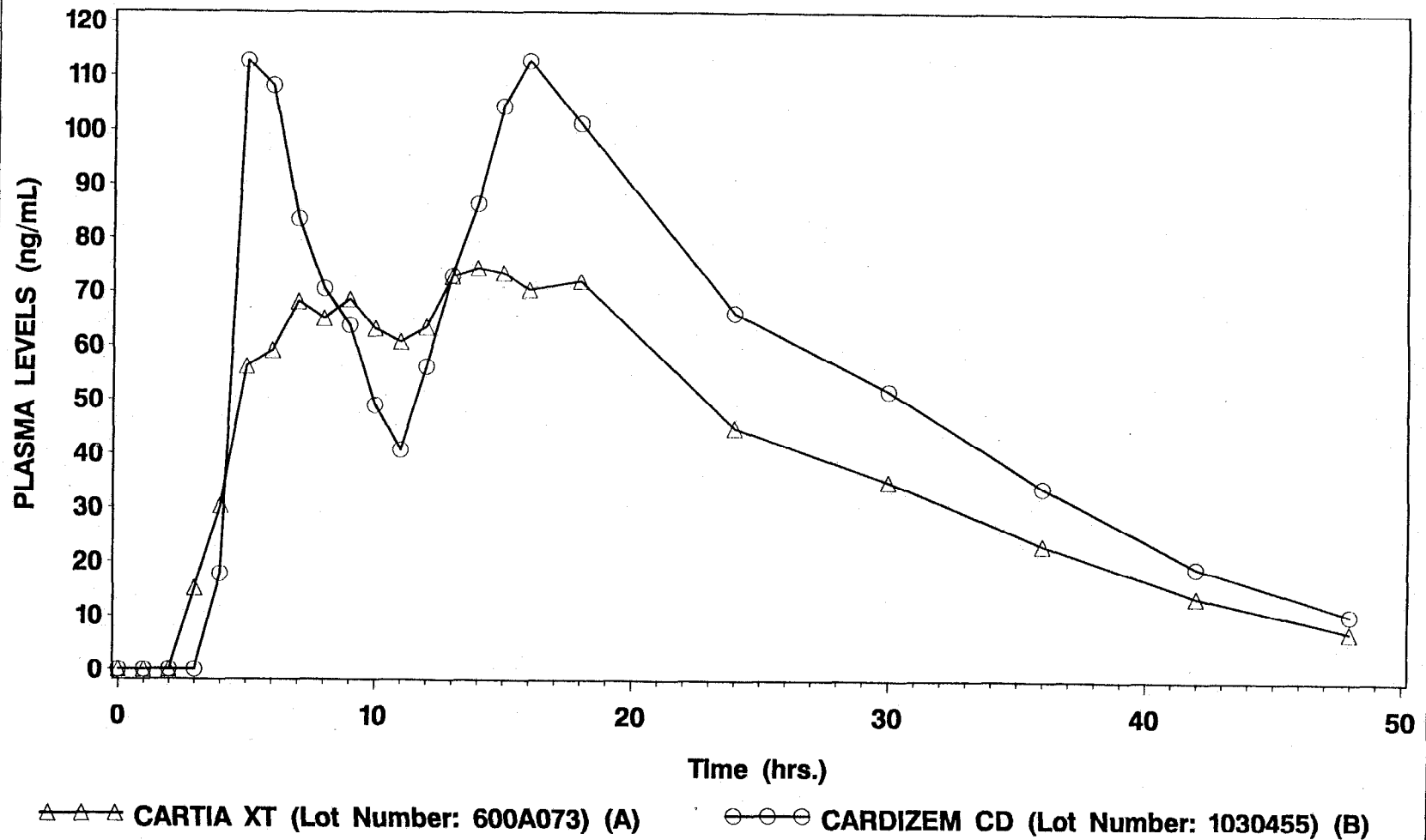


FIGURE 1.23

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 23

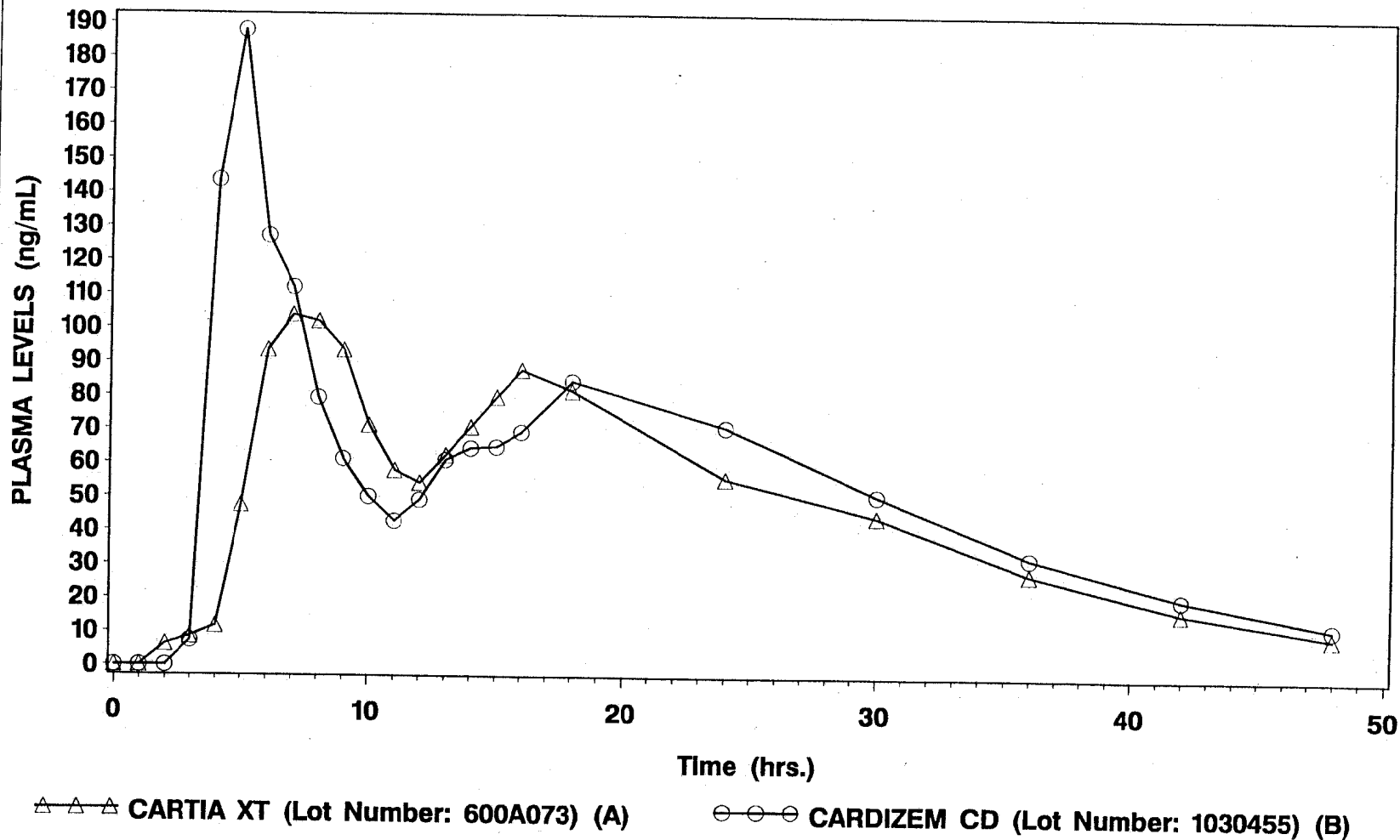


FIGURE 1.24

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 24

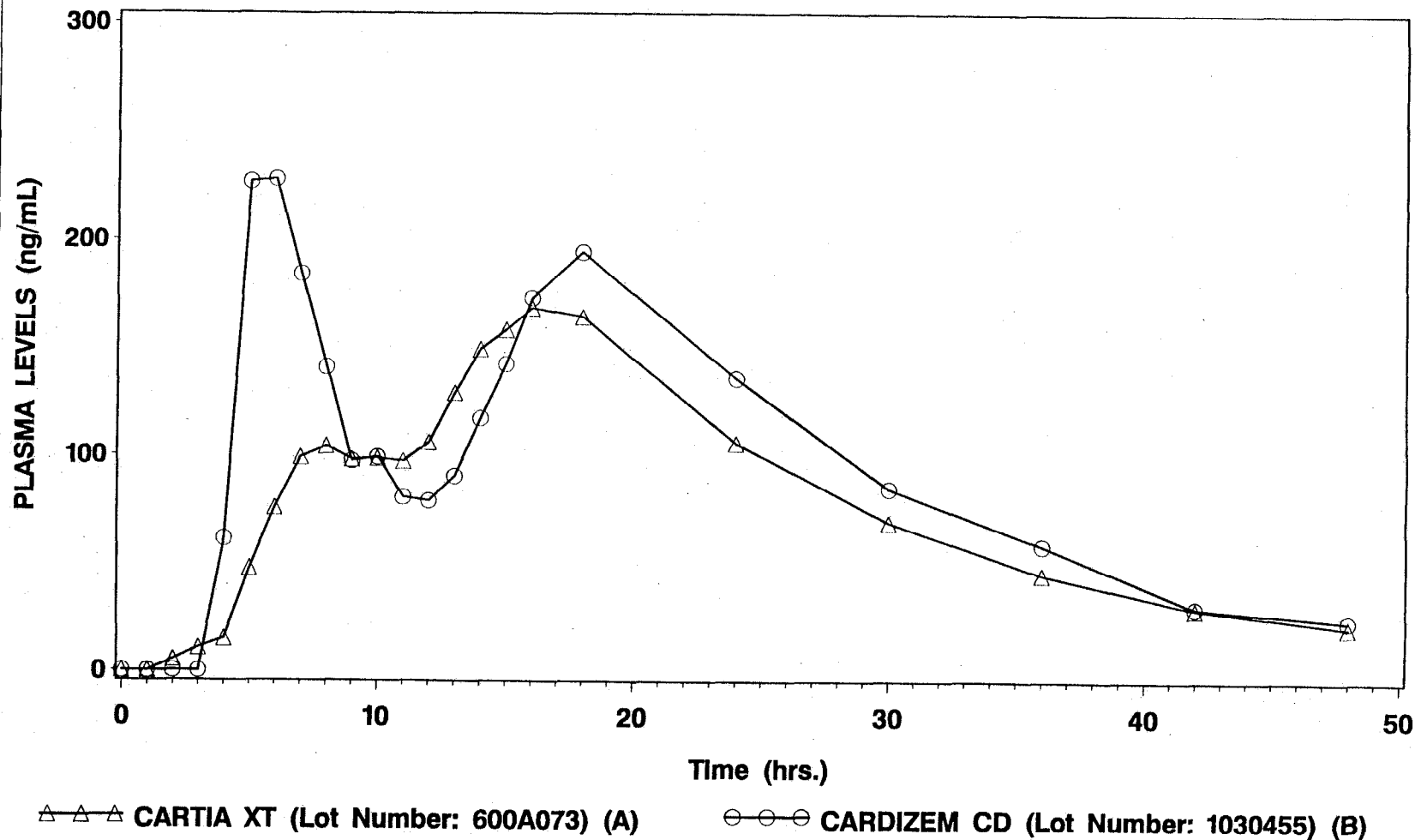


FIGURE 1.25

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 25

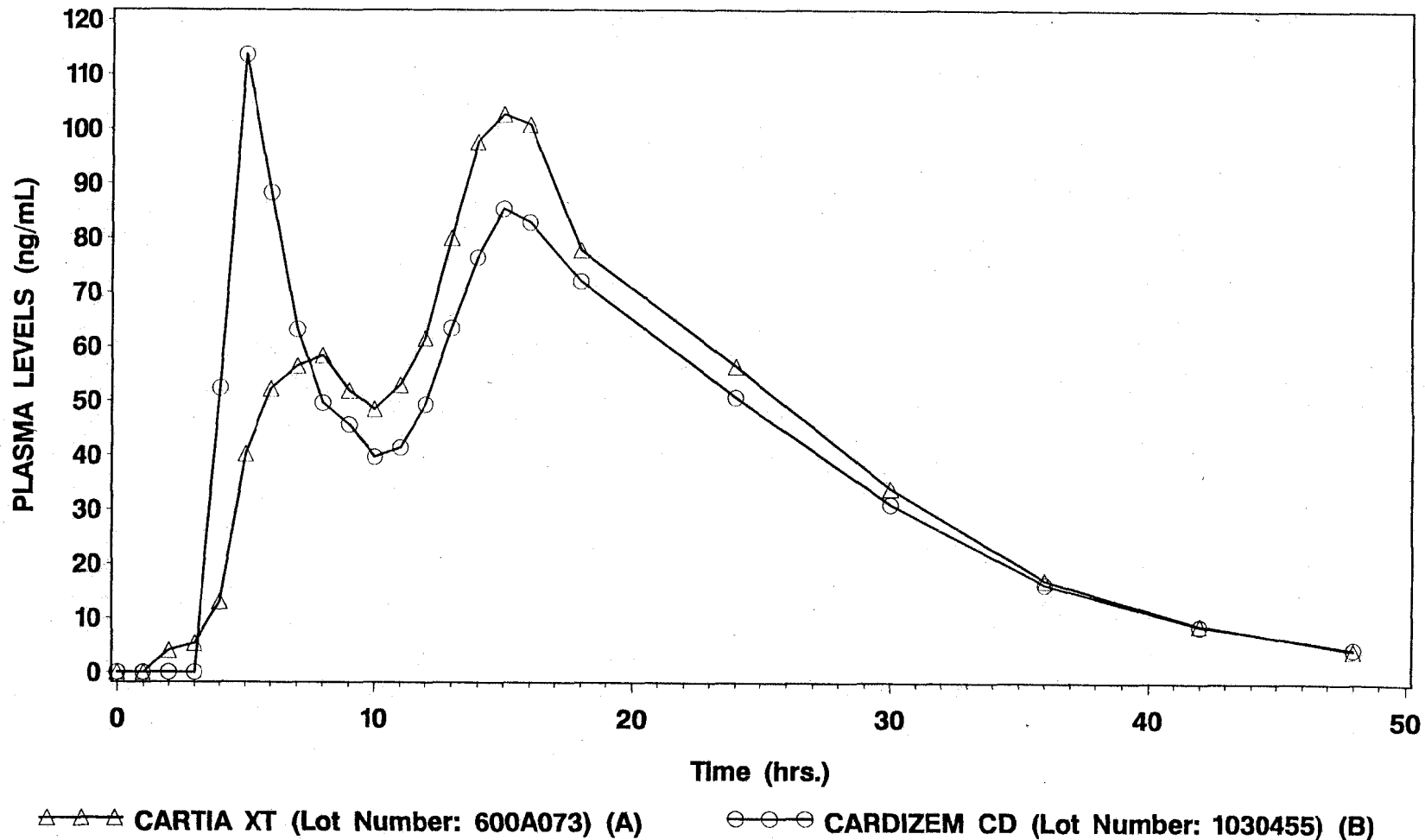


FIGURE 1.26

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 26

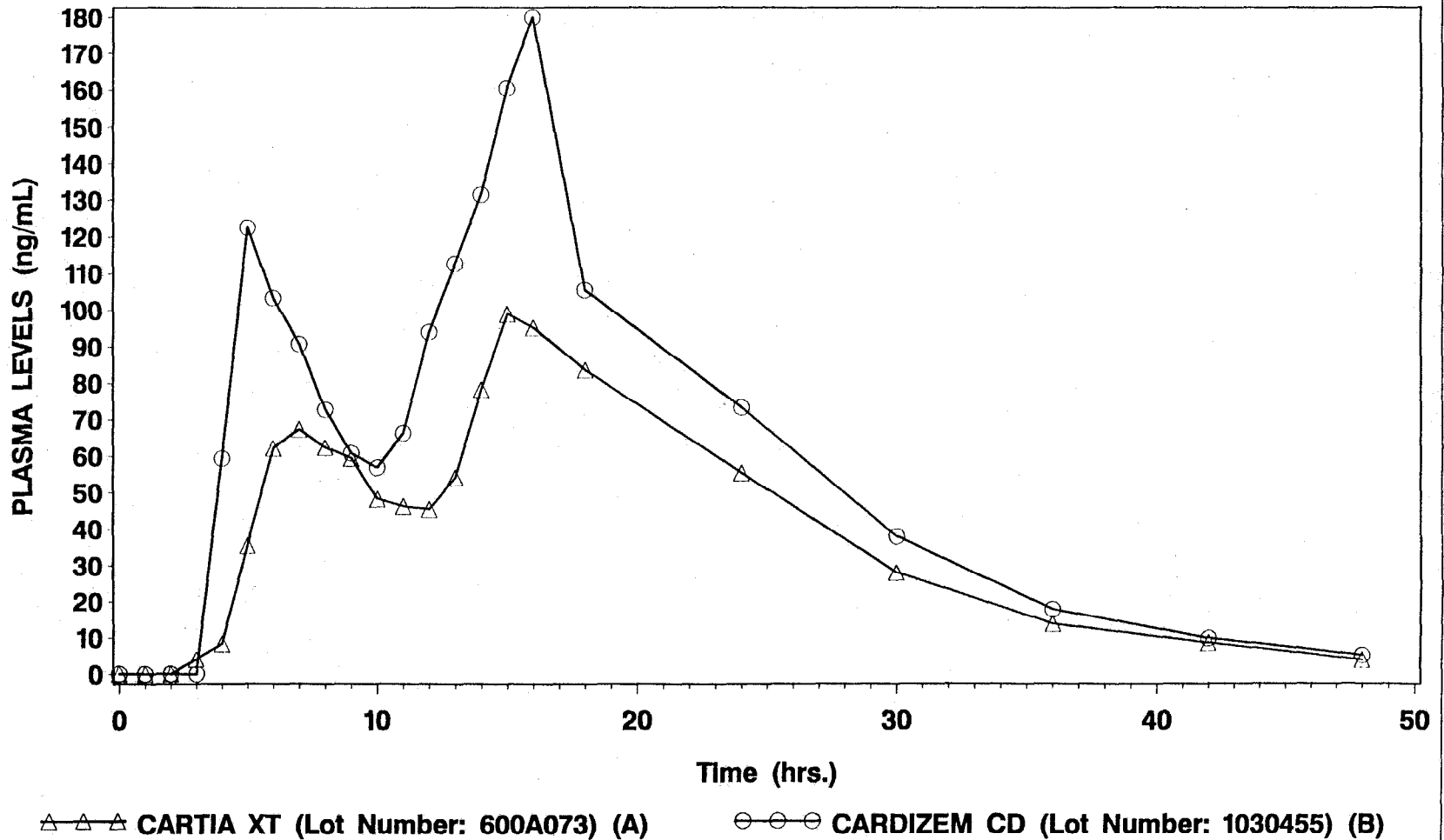


FIGURE 1.27

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 27

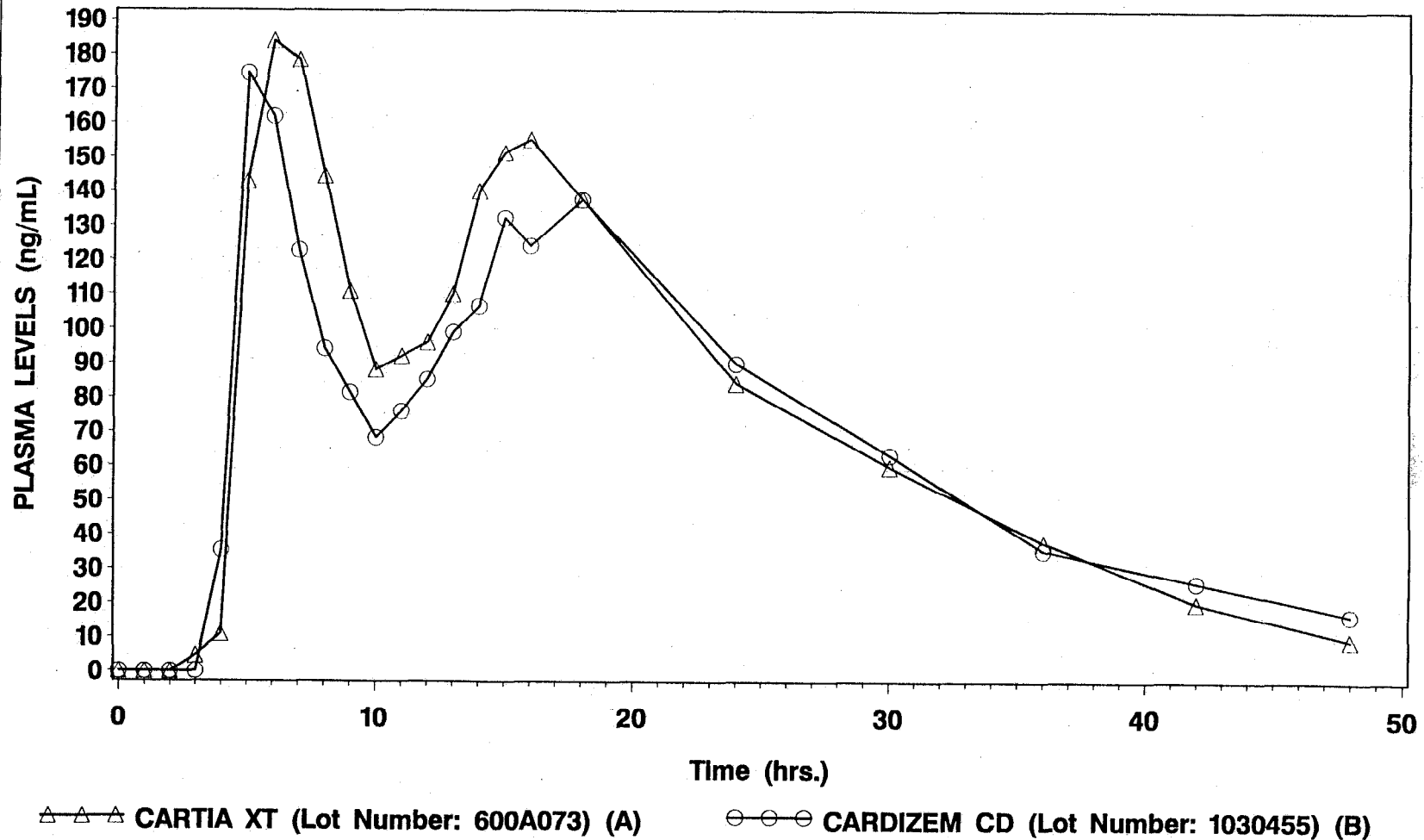


FIGURE 1.28

PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 28

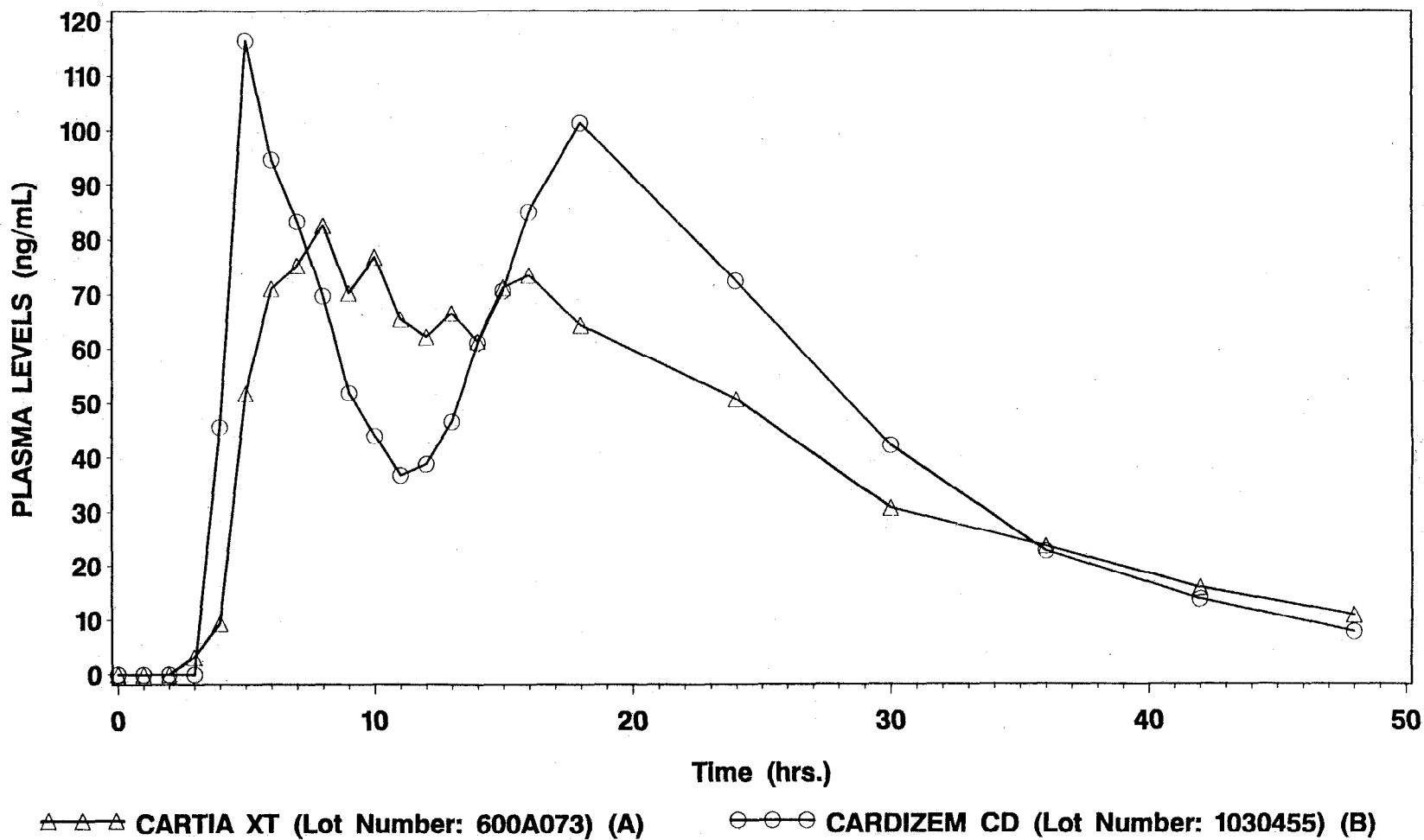


FIGURE 1.29

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 01

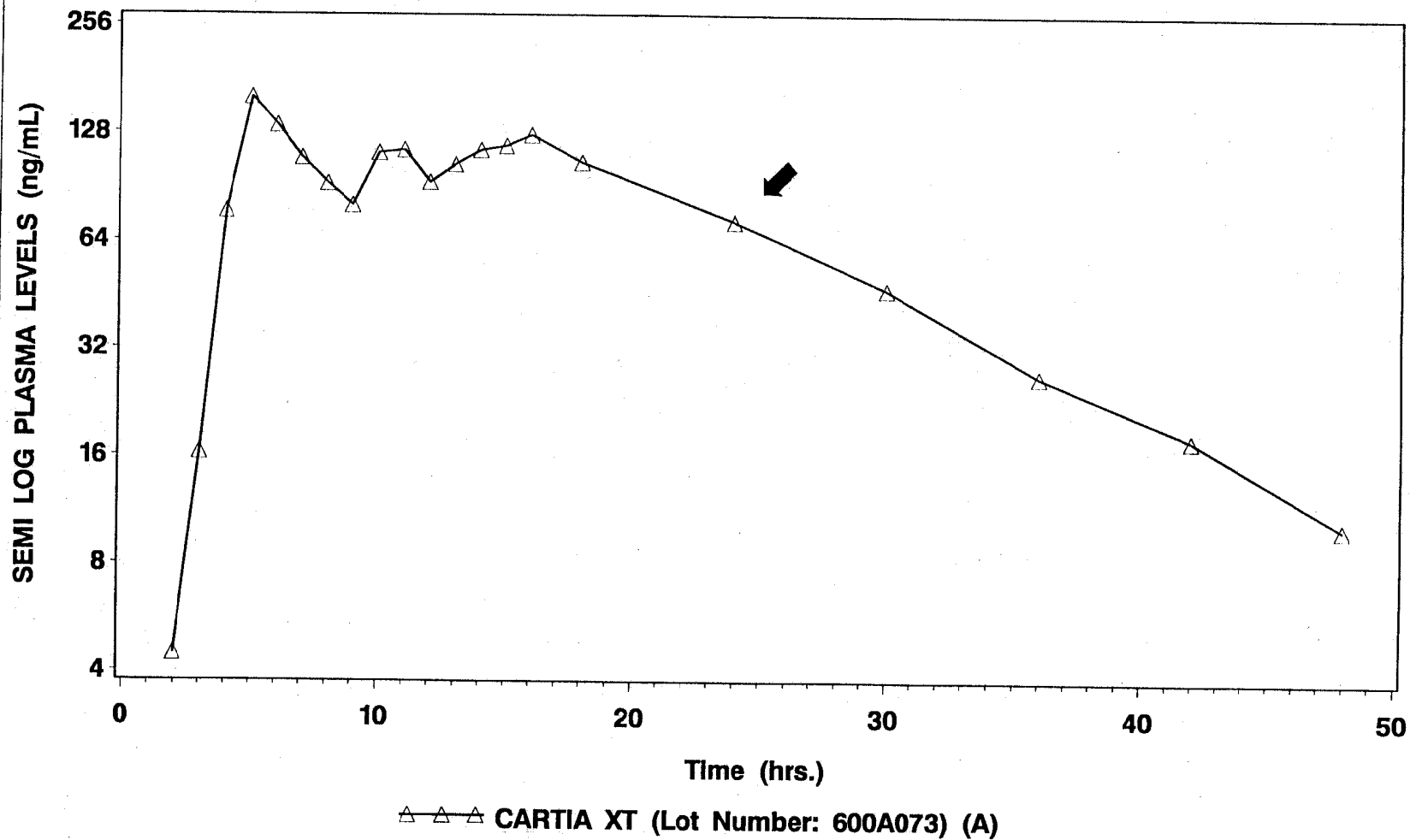


FIGURE 1.30

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=03

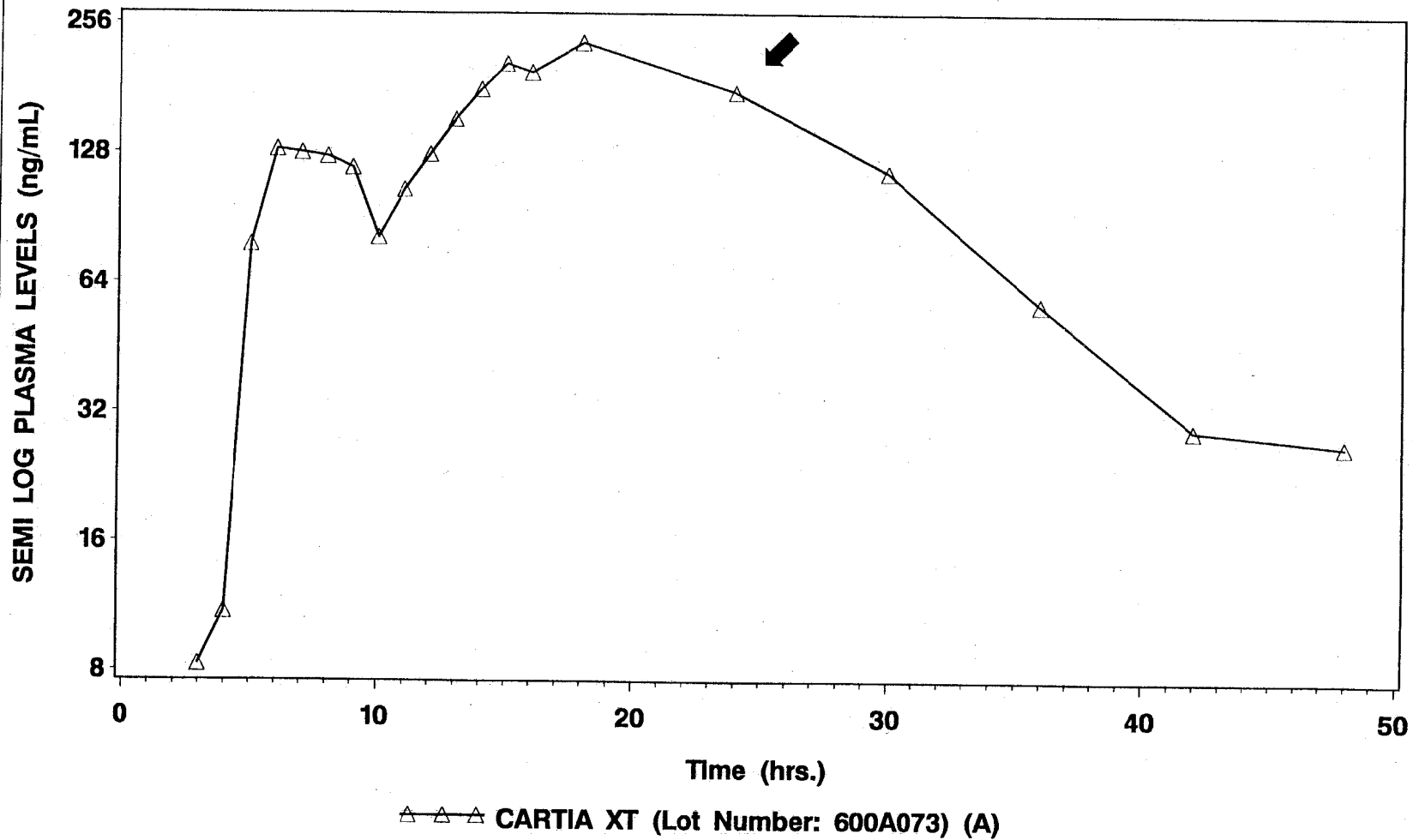


FIGURE 1.31

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 04

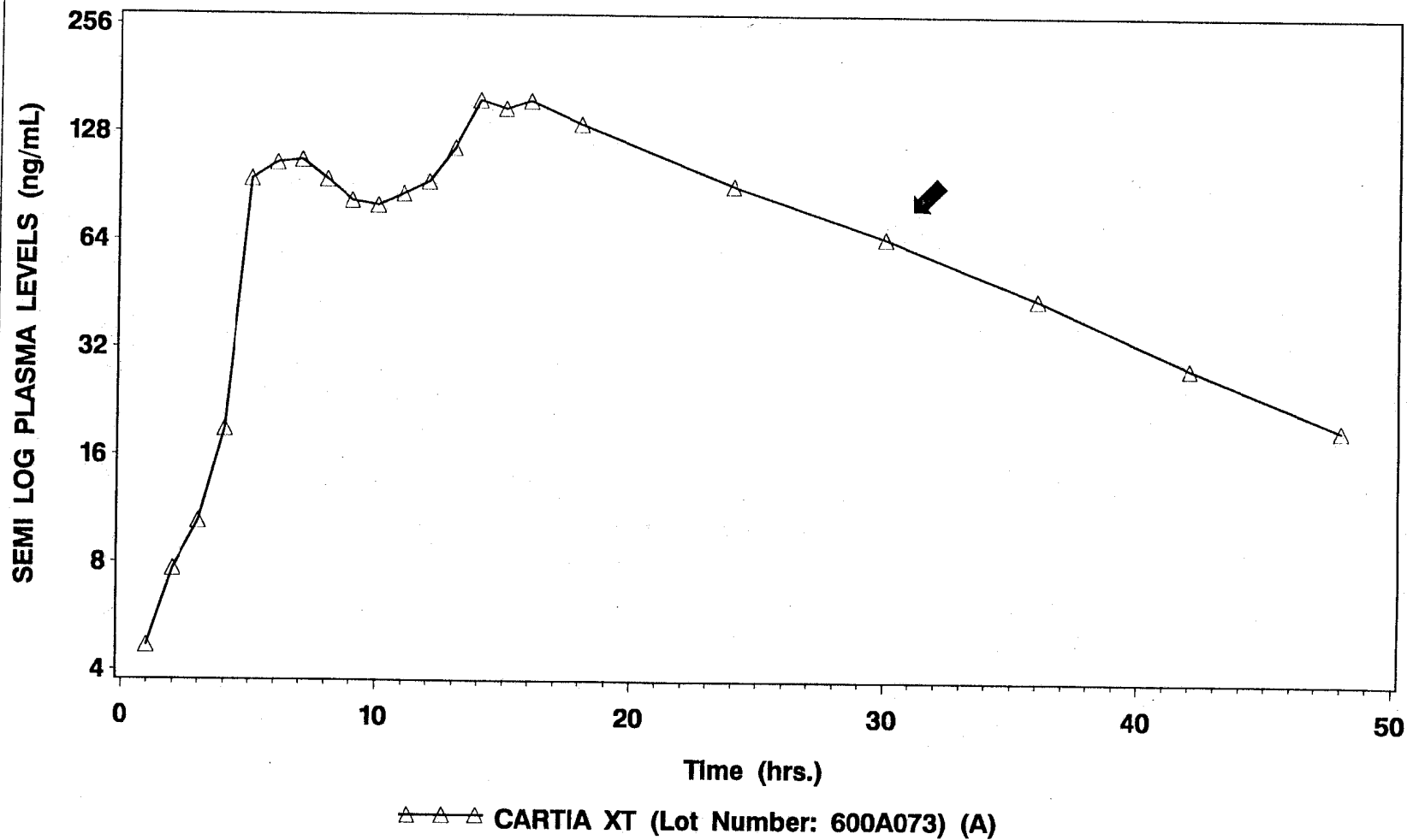


FIGURE 1.32

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 05

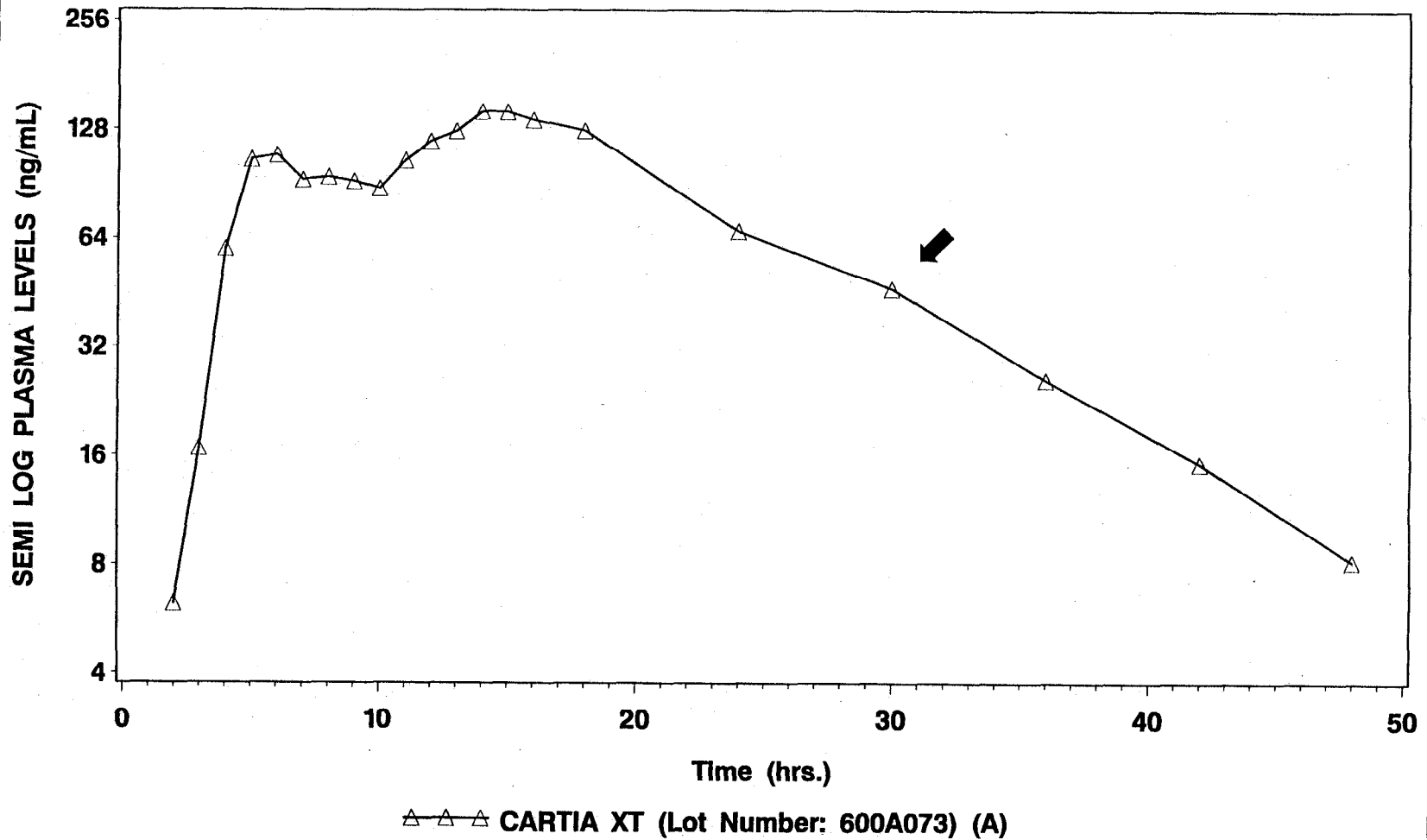


FIGURE 1.33

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 06

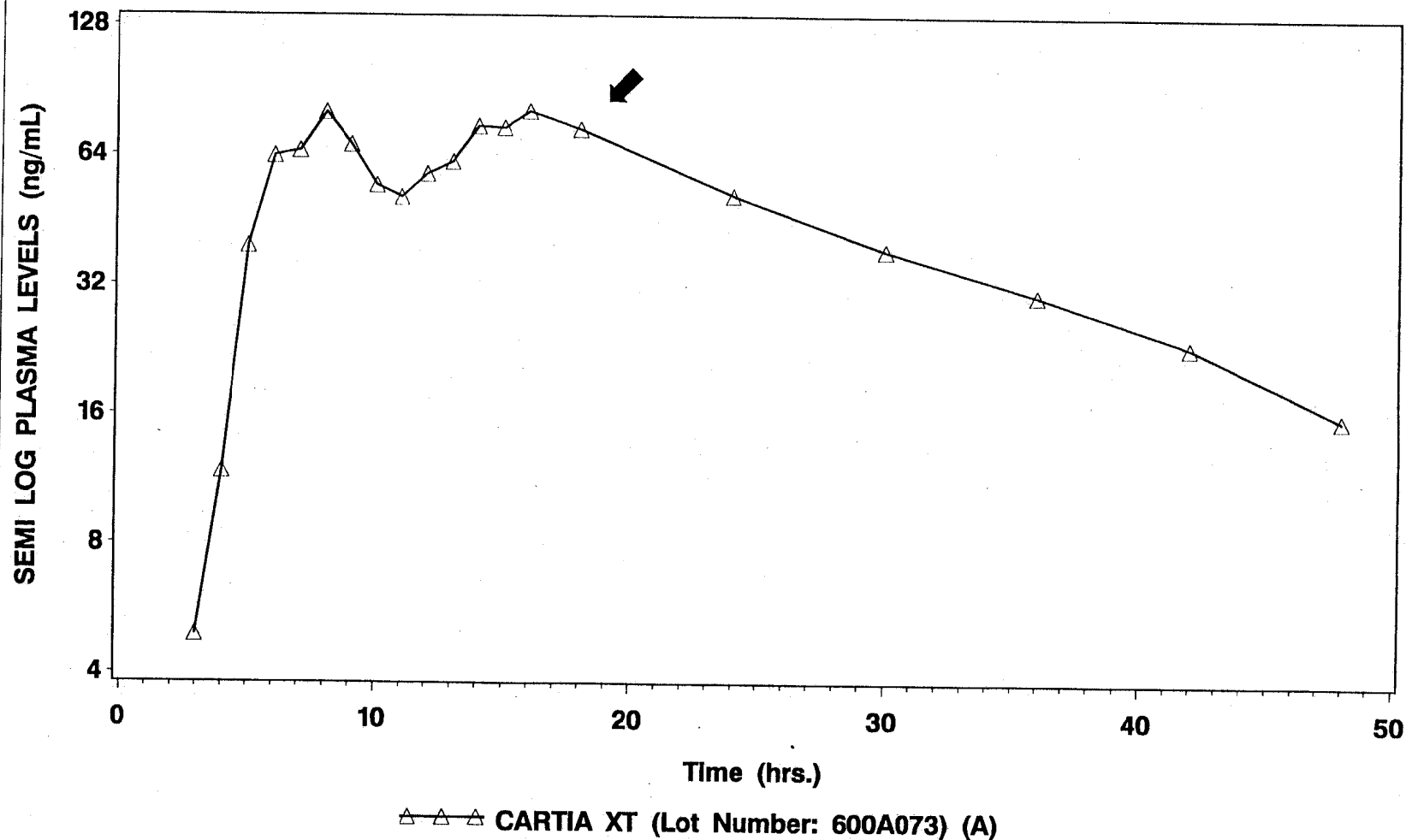
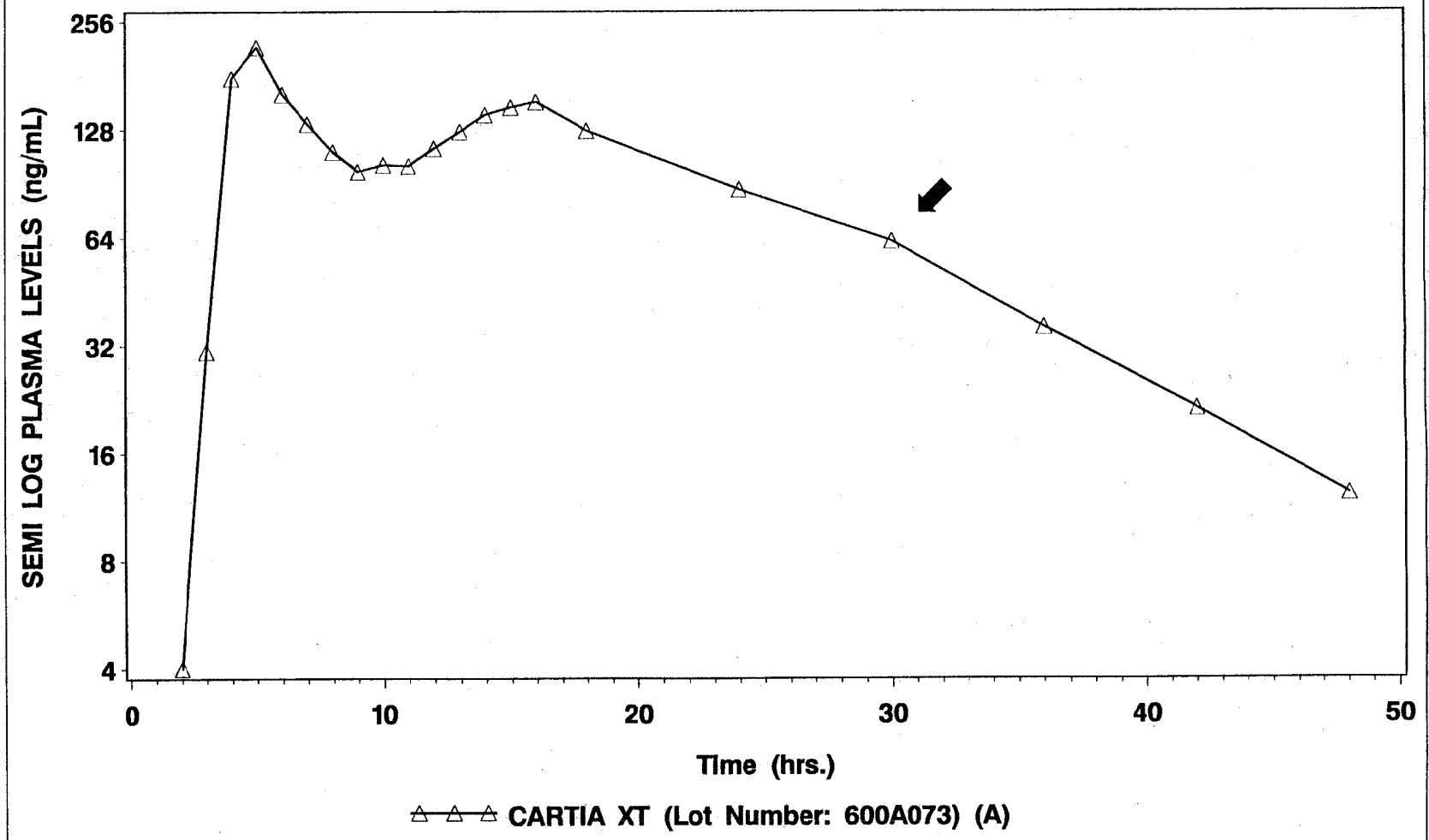


FIGURE 1.34

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 07



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 1.35

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 08

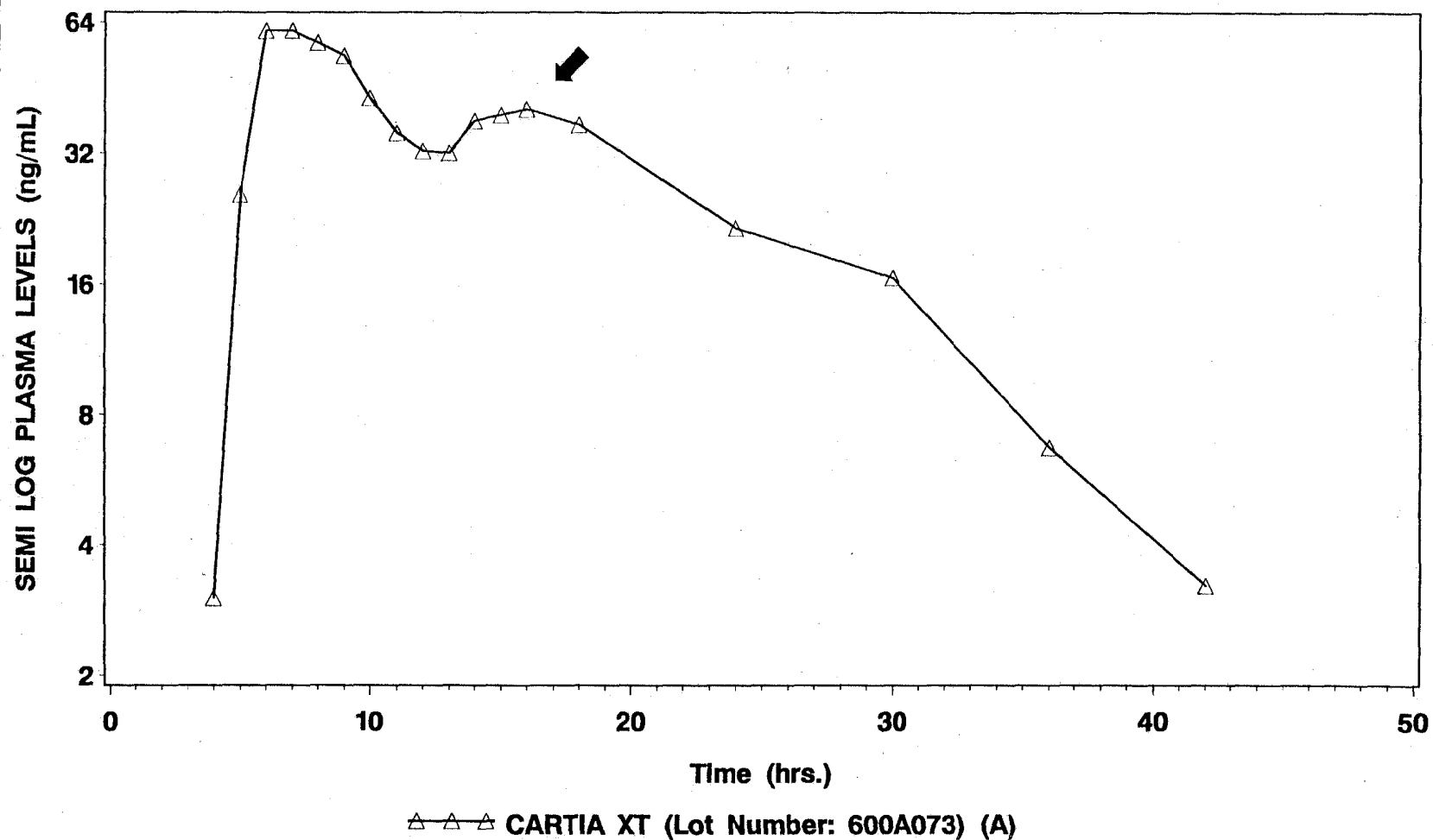
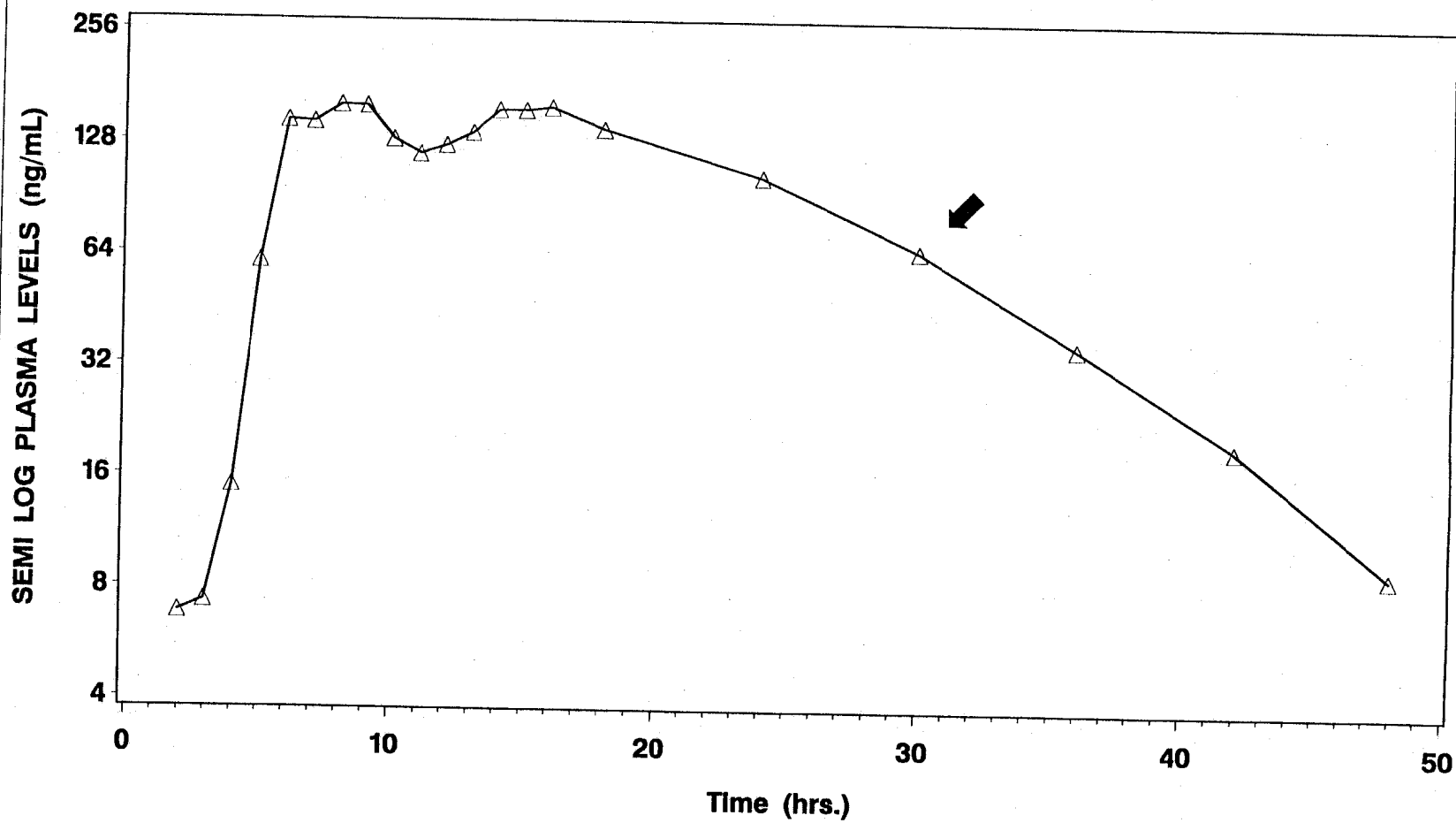


FIGURE 1.36

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=09



△—△—△ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 1.37

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=10

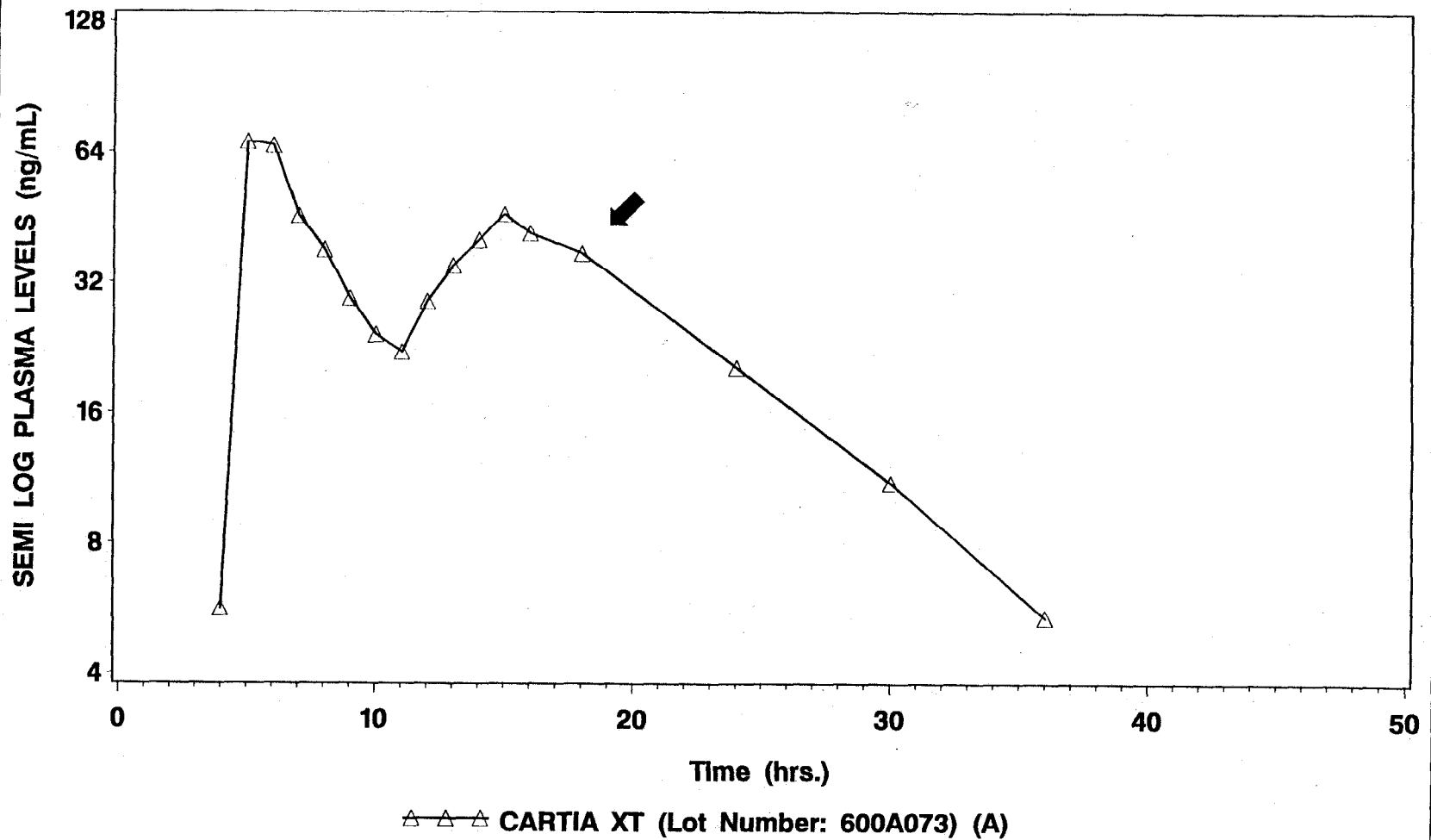
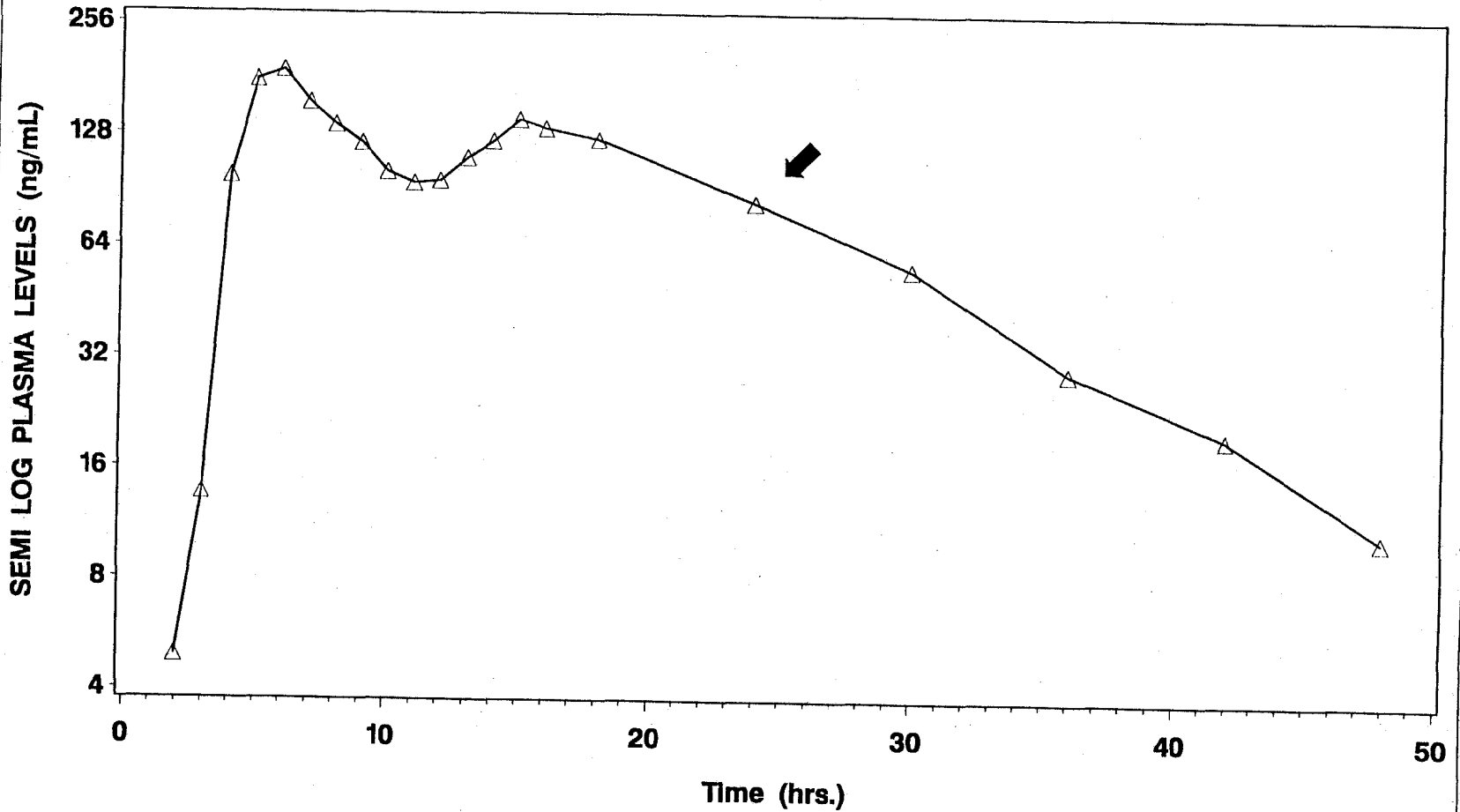


FIGURE 1.38

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 11



△△△ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 1.39

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 12

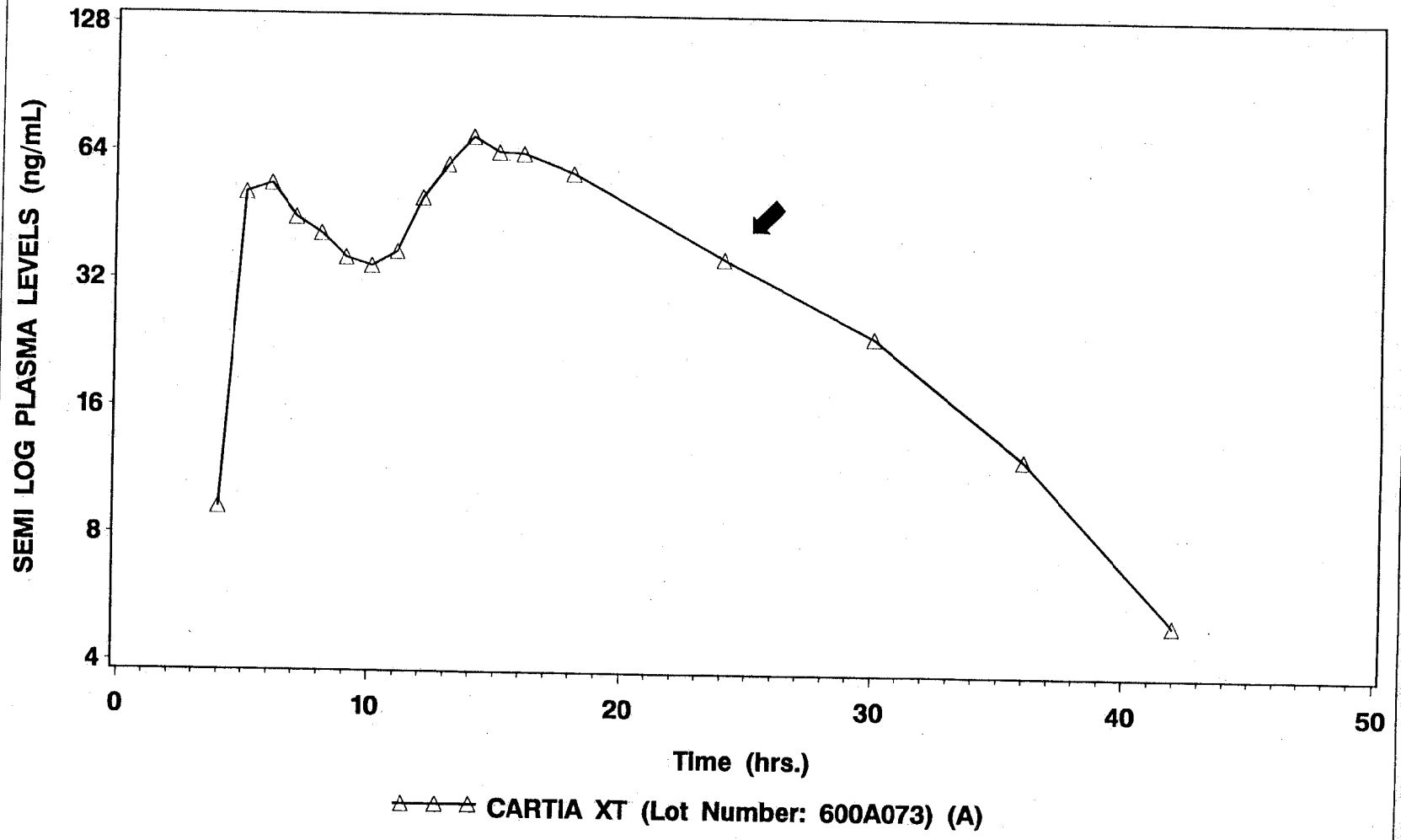


FIGURE 1.40

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 13

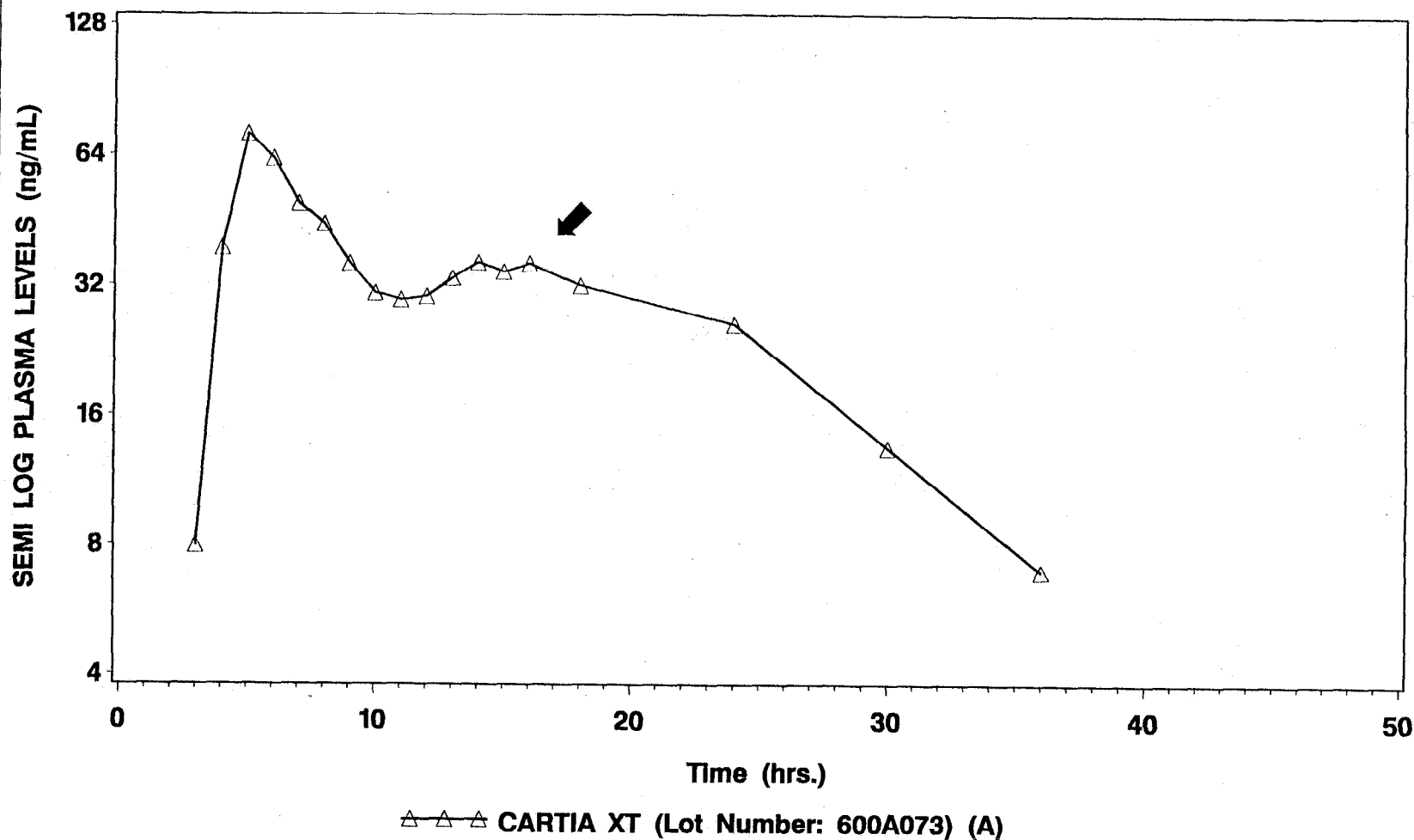


FIGURE 1.41

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 14

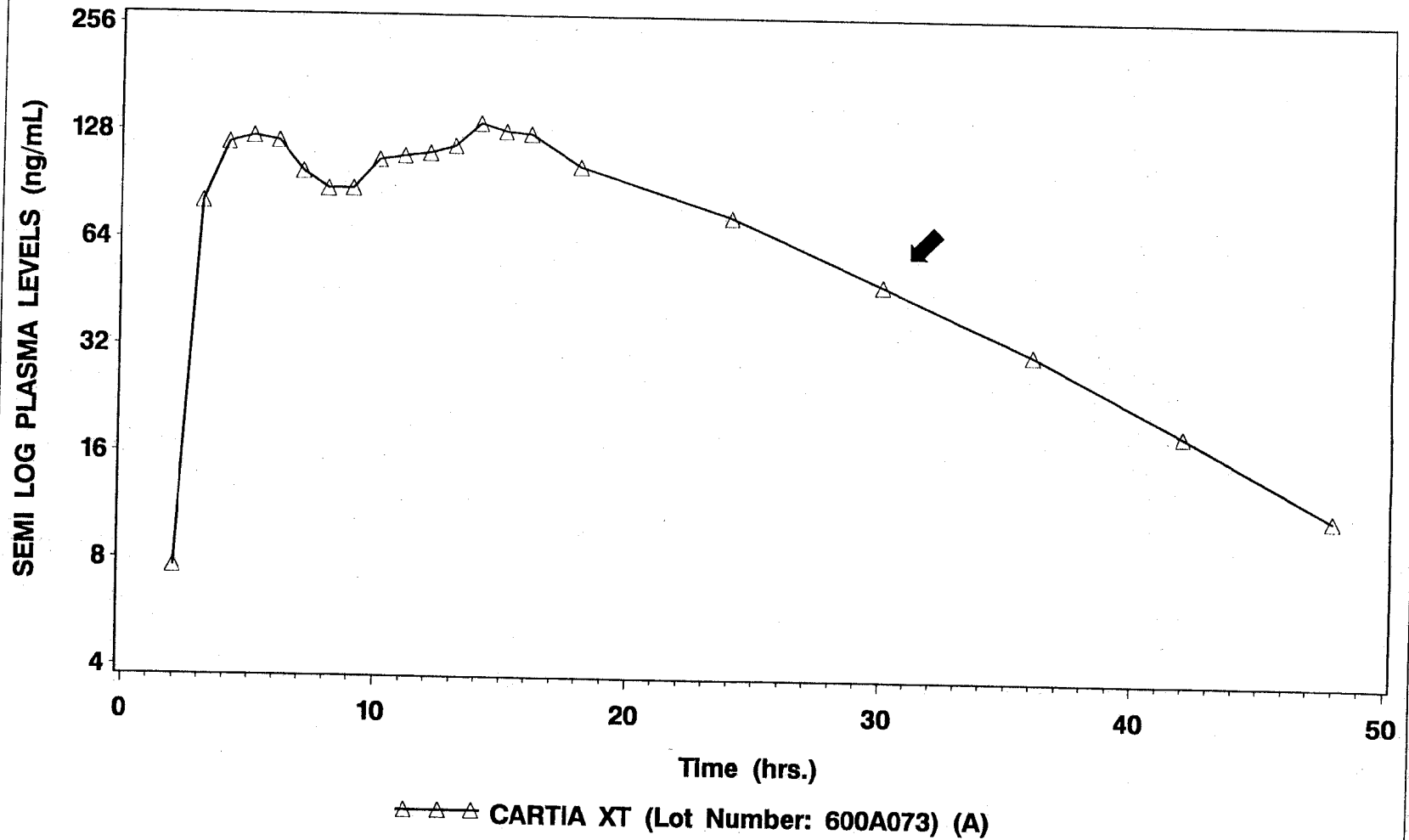


FIGURE 1.42

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 15

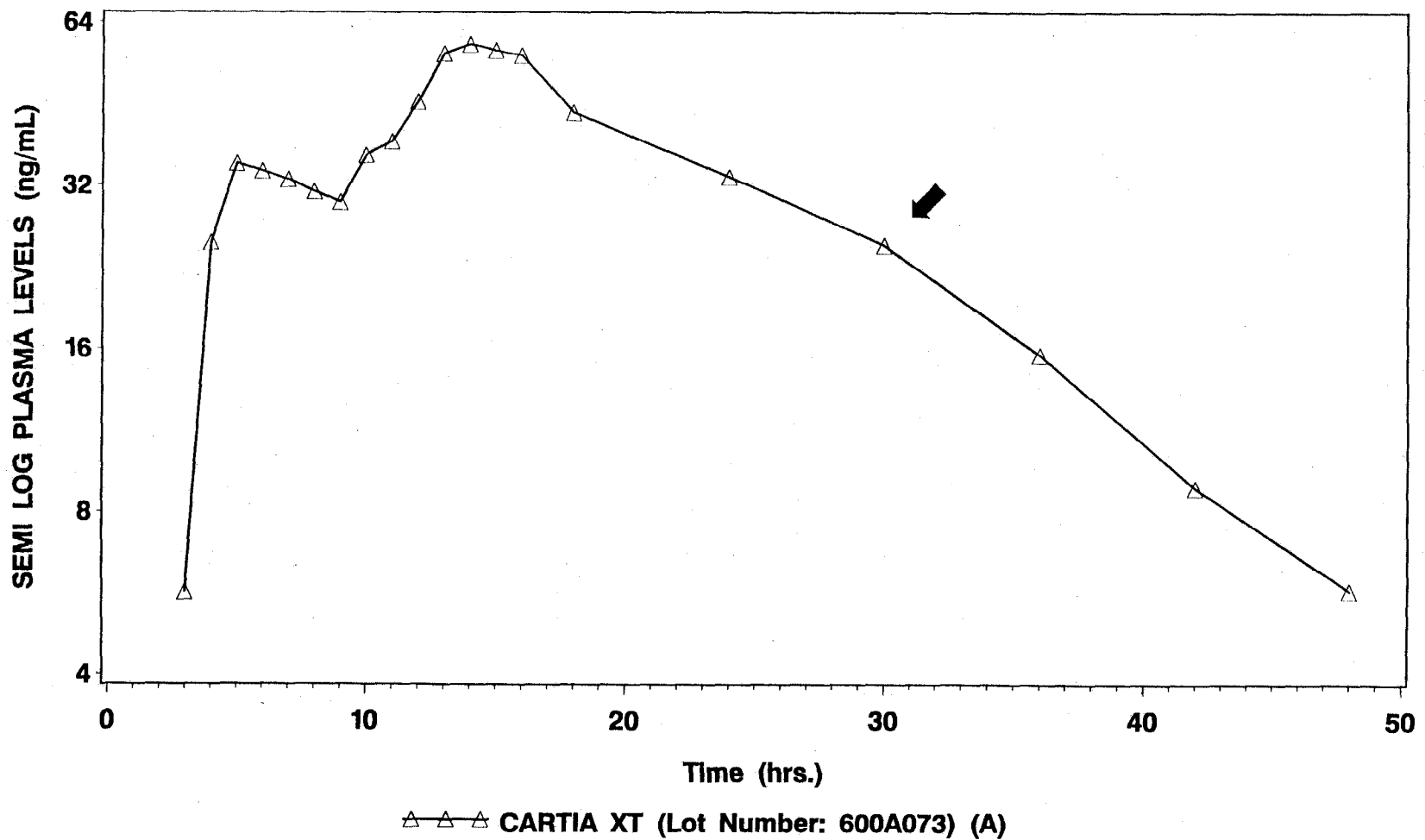


FIGURE 1.43

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 16

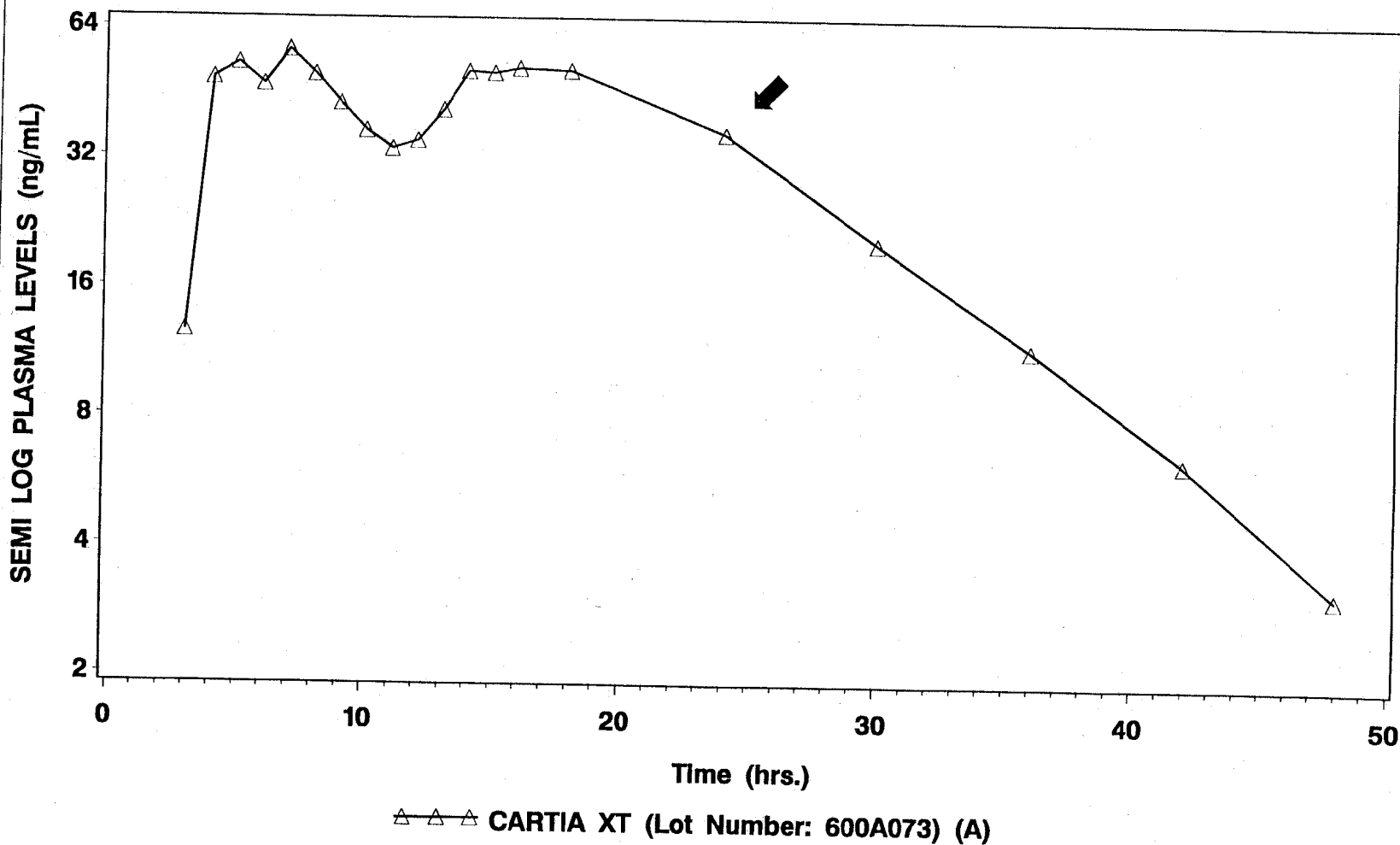


FIGURE 1.44

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 17

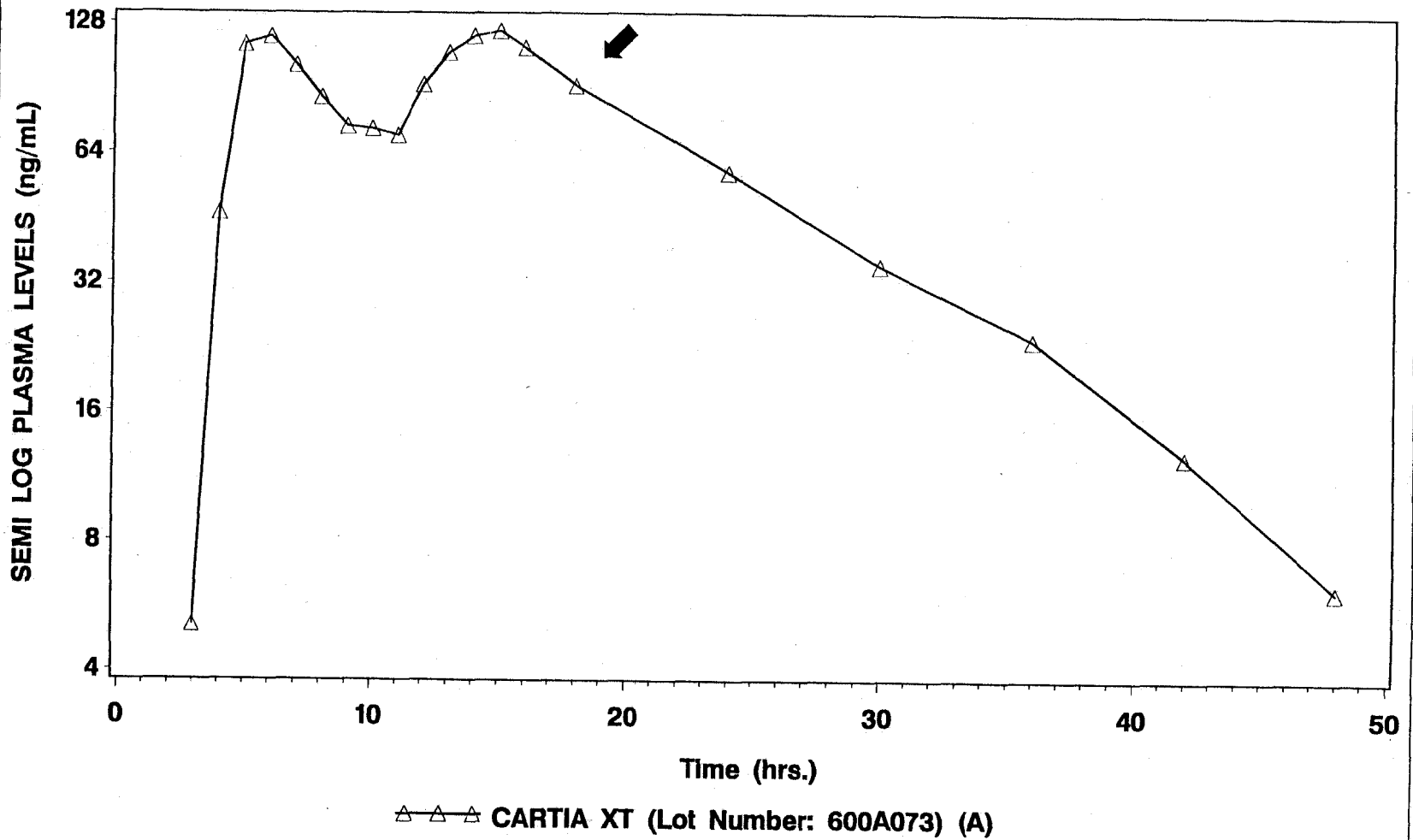


FIGURE 1.45

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=18

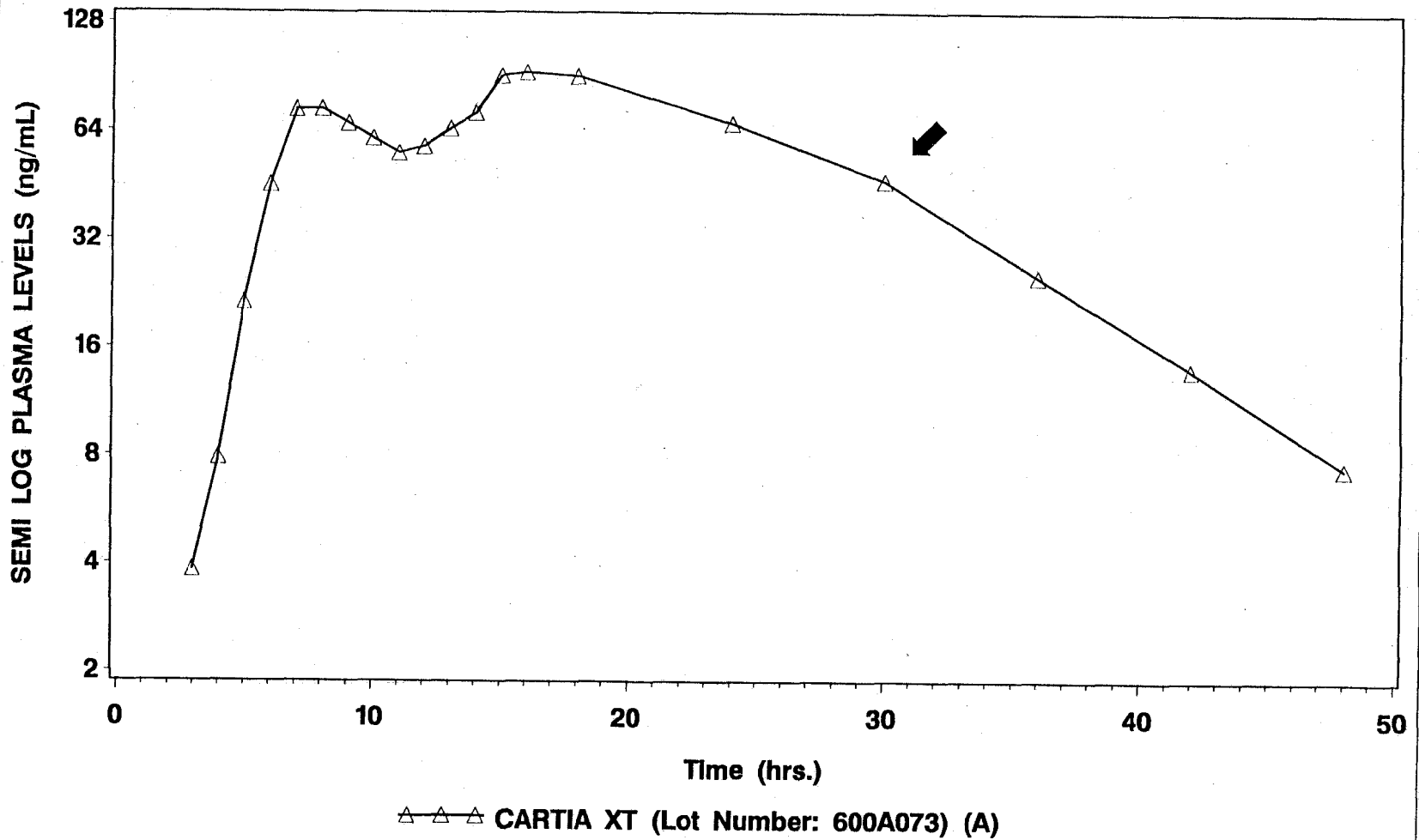


FIGURE 1.46

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 19

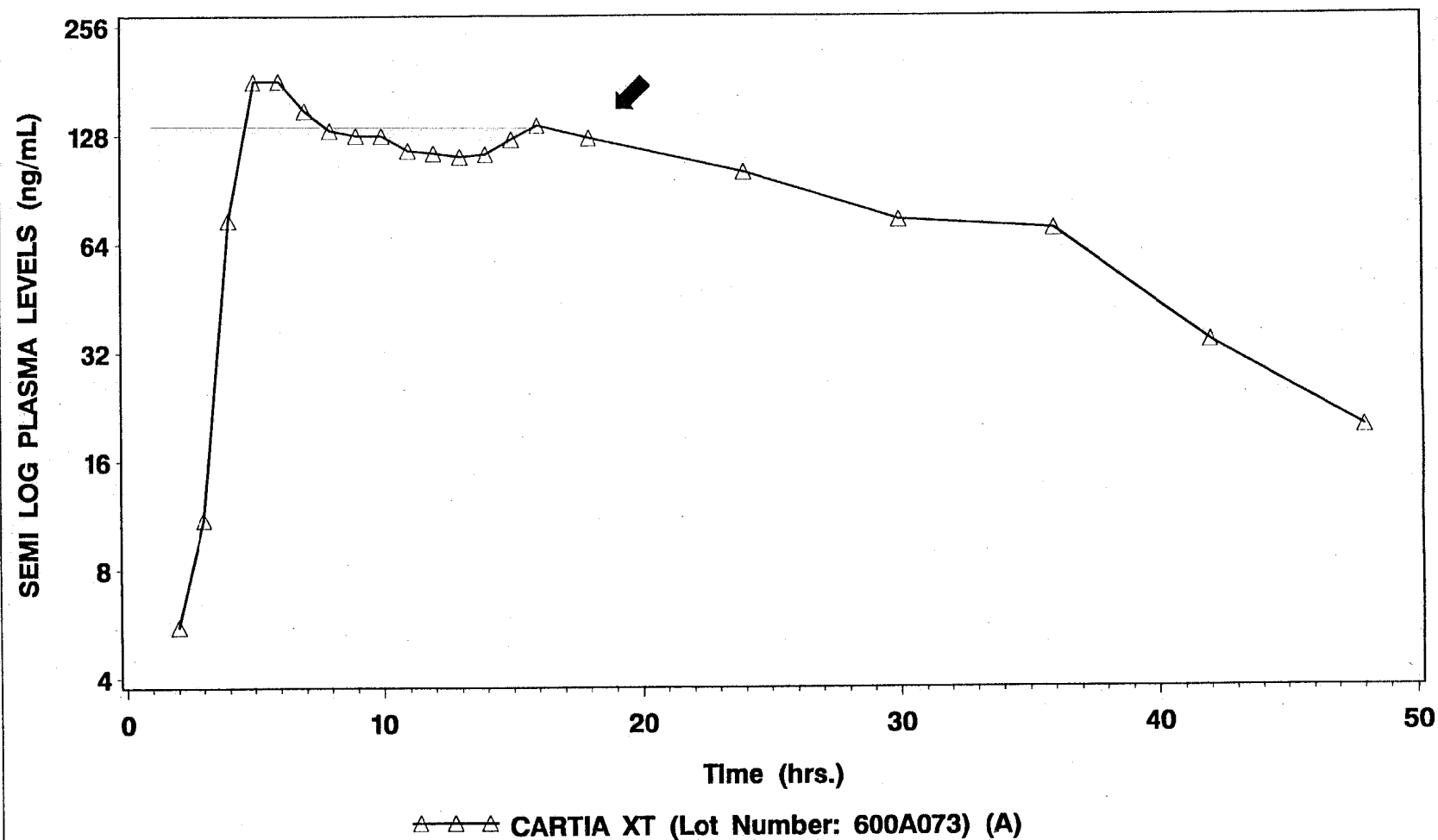


FIGURE 1.47

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 20

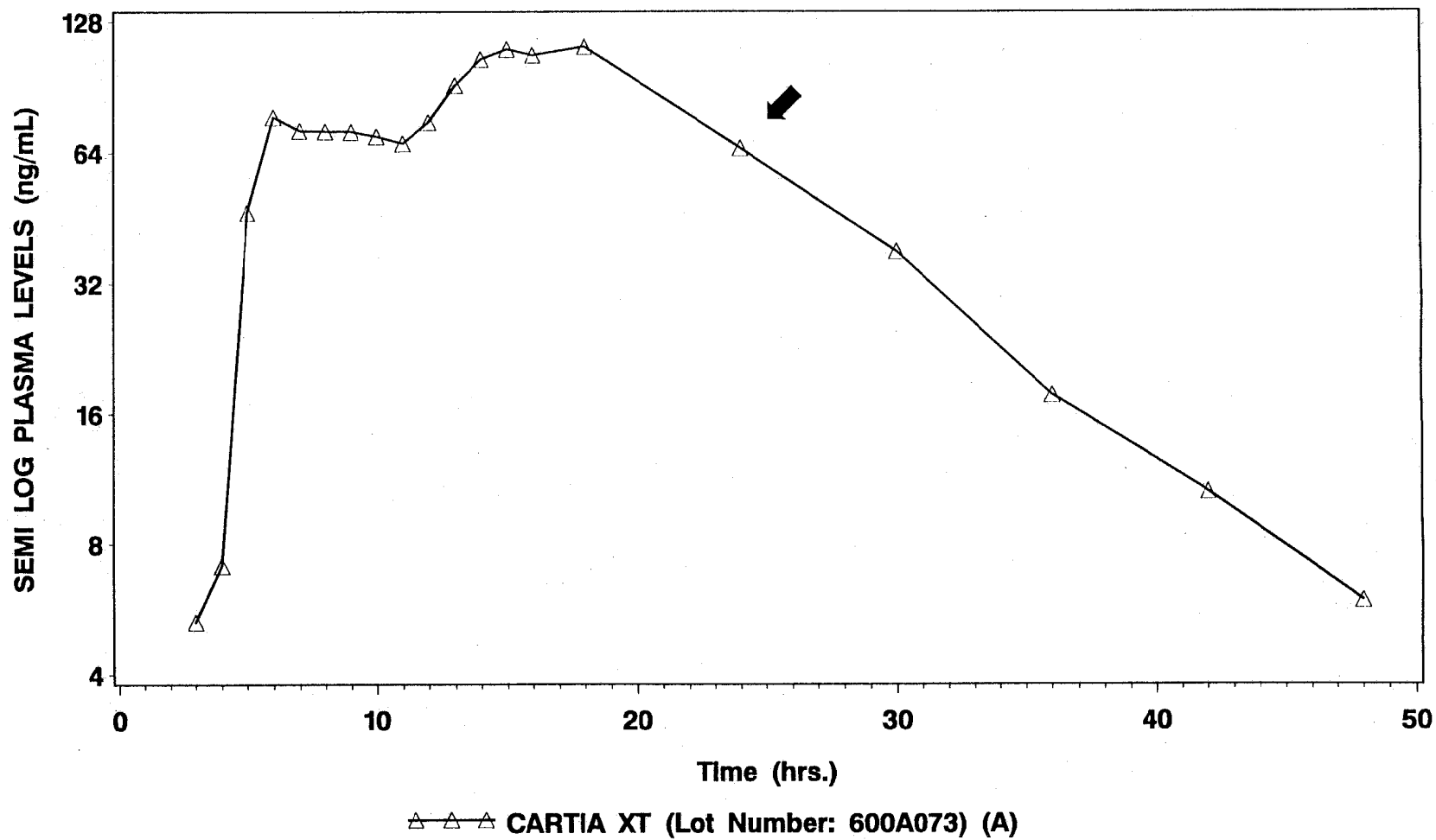


FIGURE 1.48

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 21

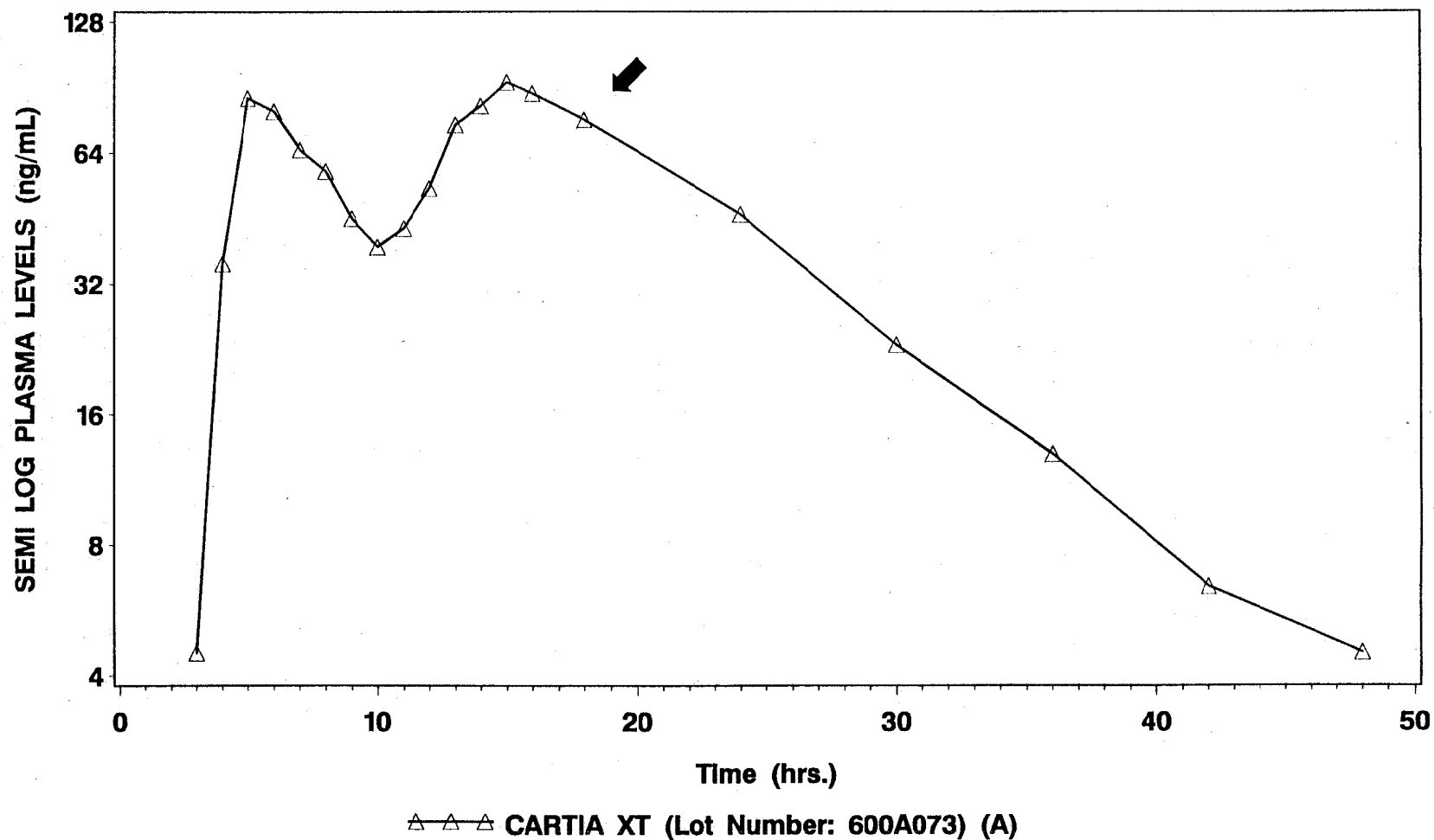
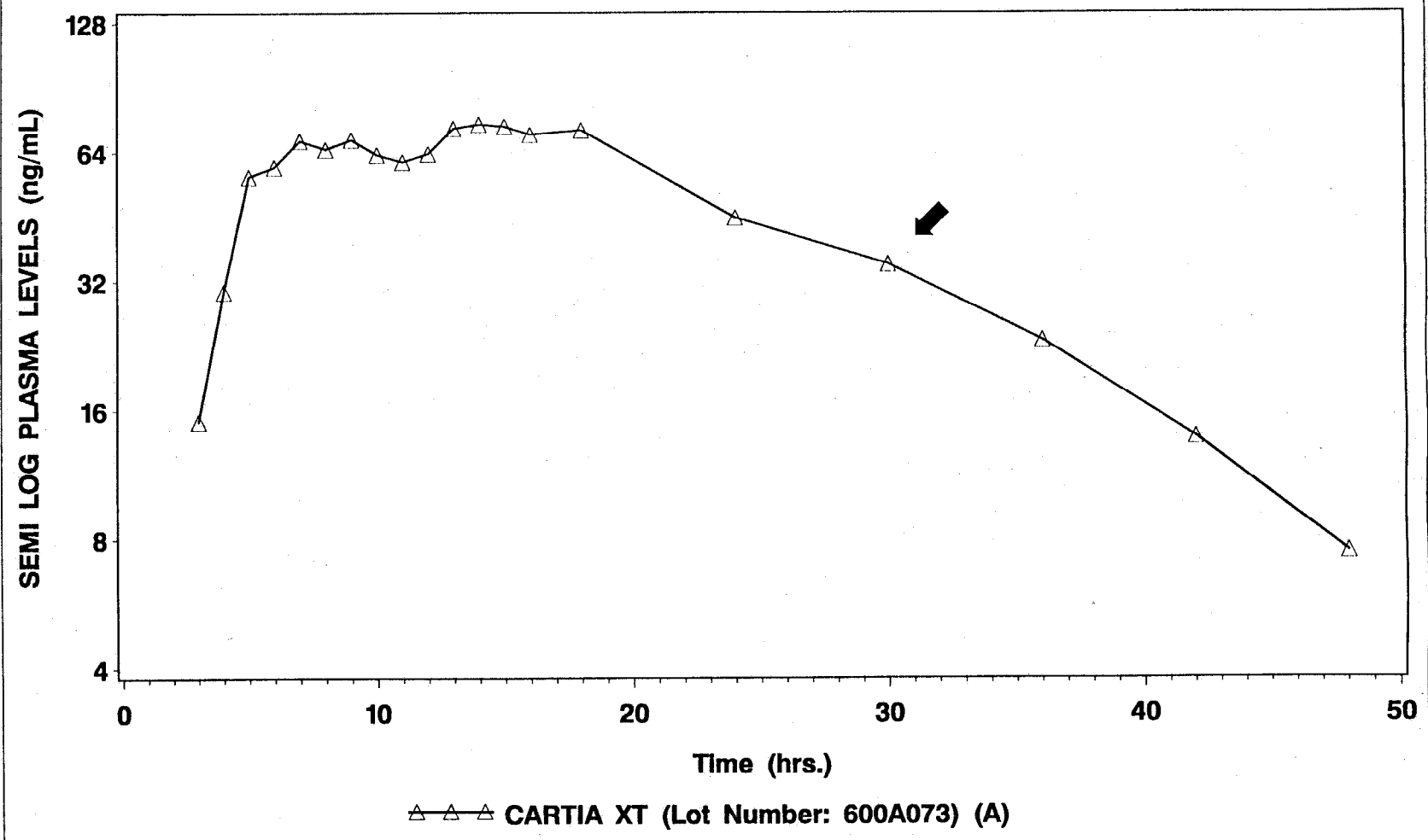


FIGURE 1.49

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 22



△—△ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 1.50

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 23

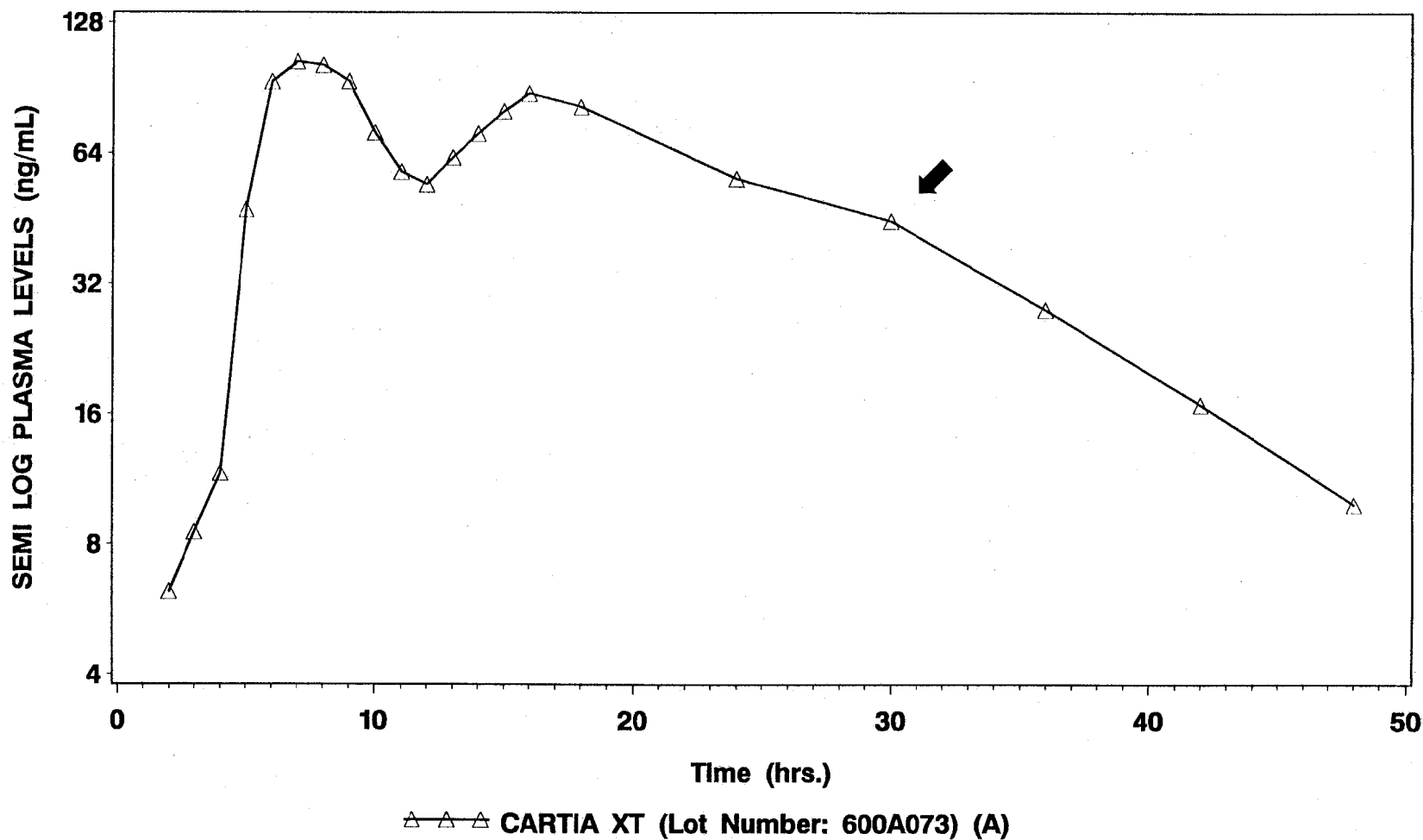


FIGURE 1.51

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 24

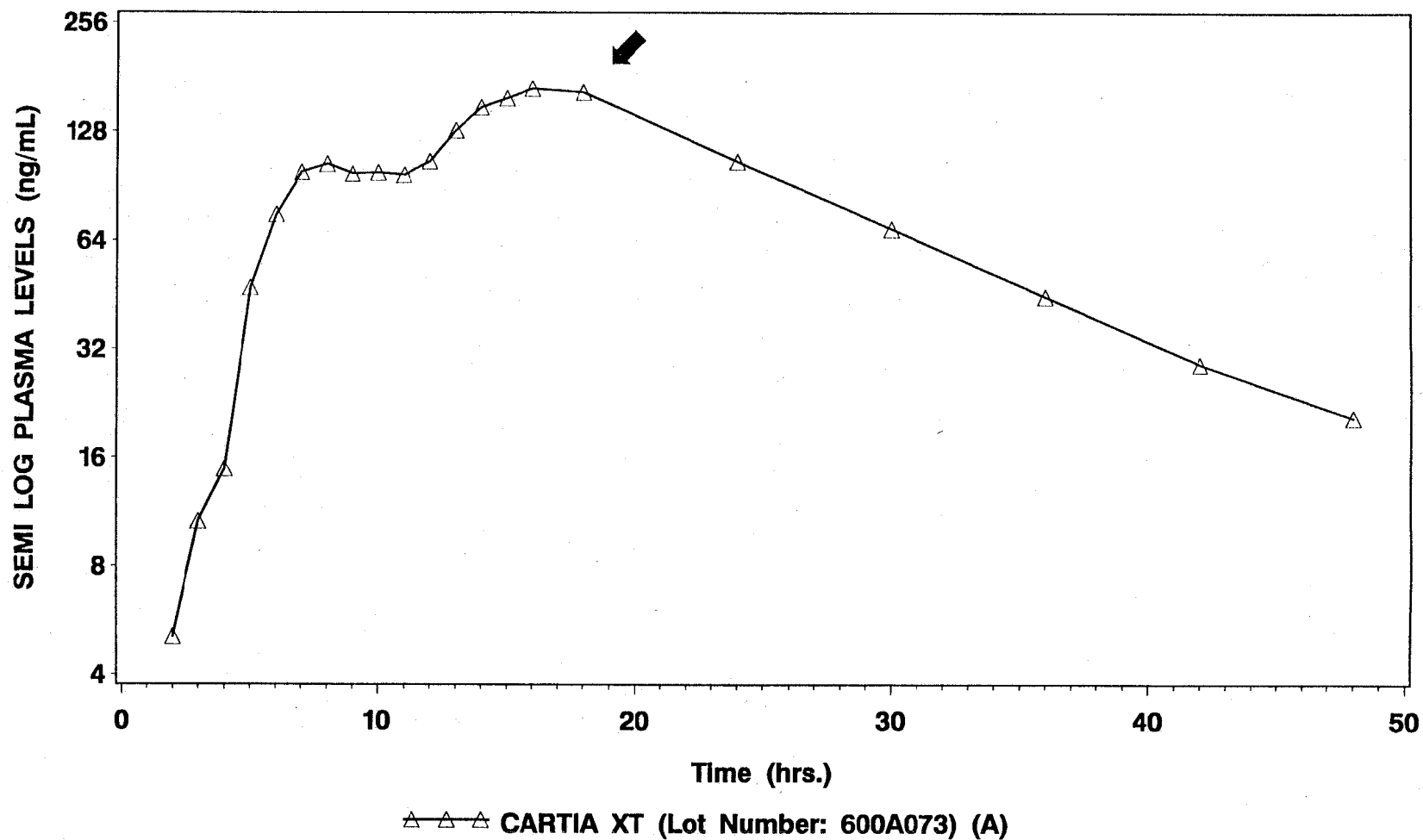


FIGURE 1.52

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 25

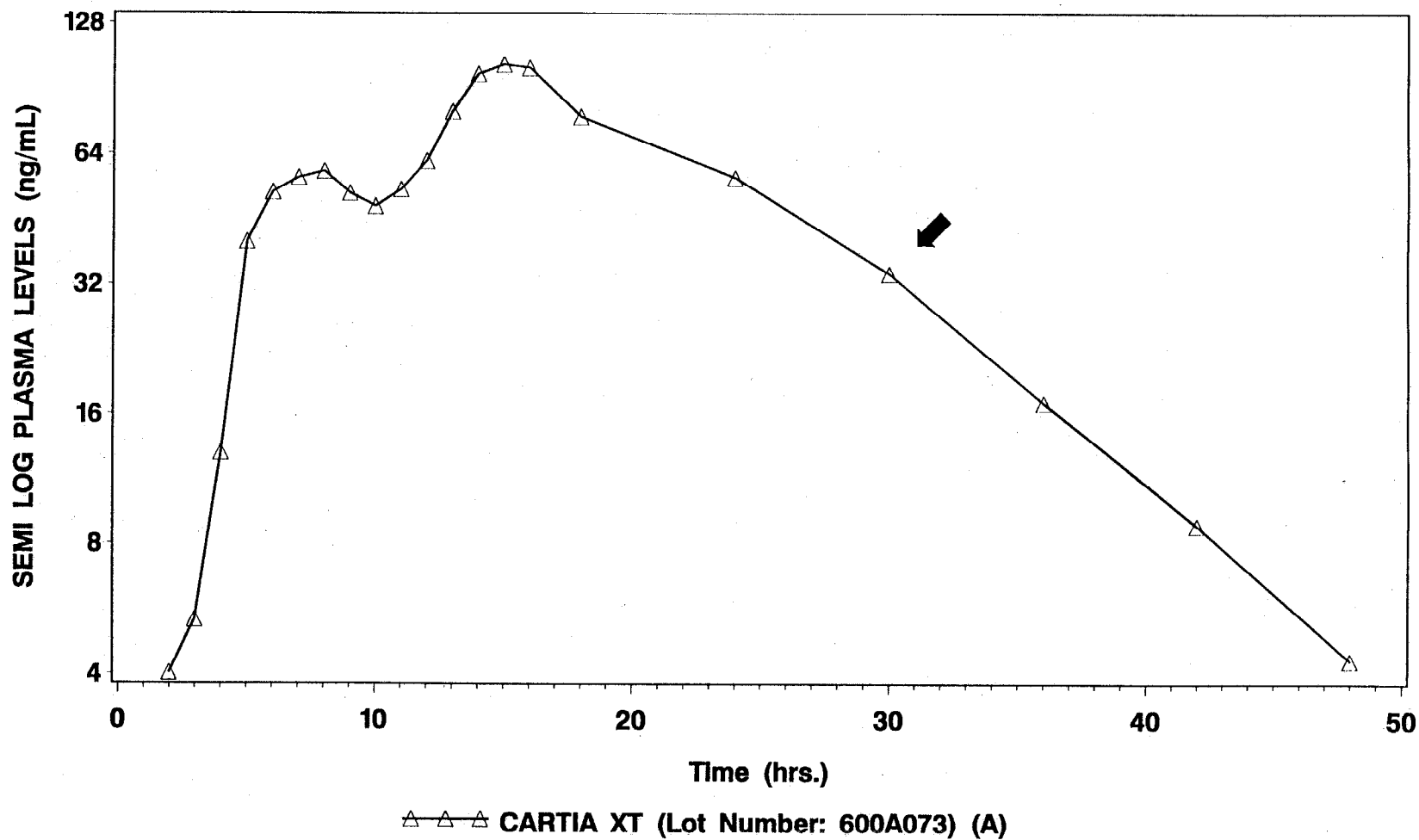


FIGURE 1.53

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 26

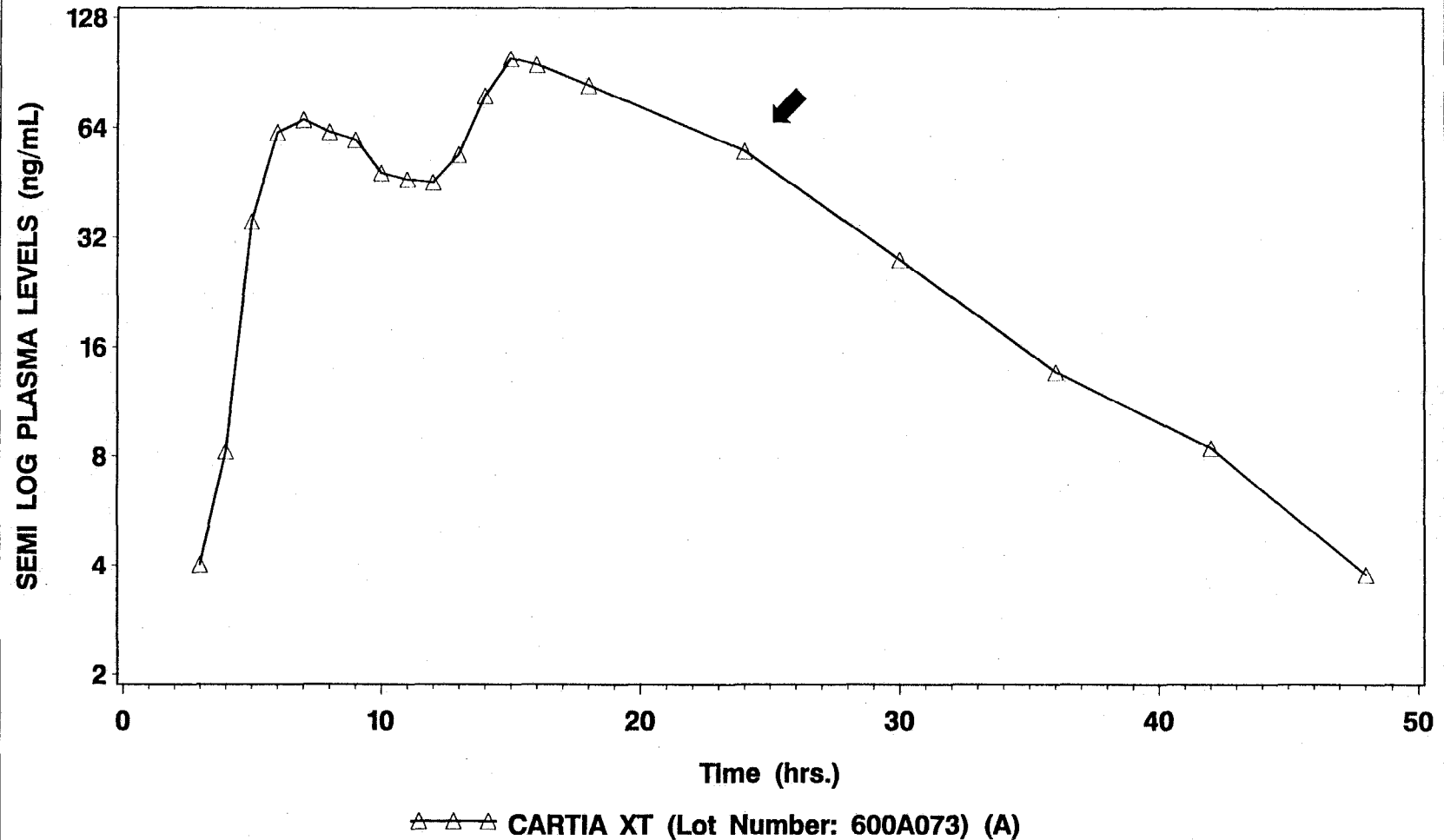


FIGURE 1.54

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 27

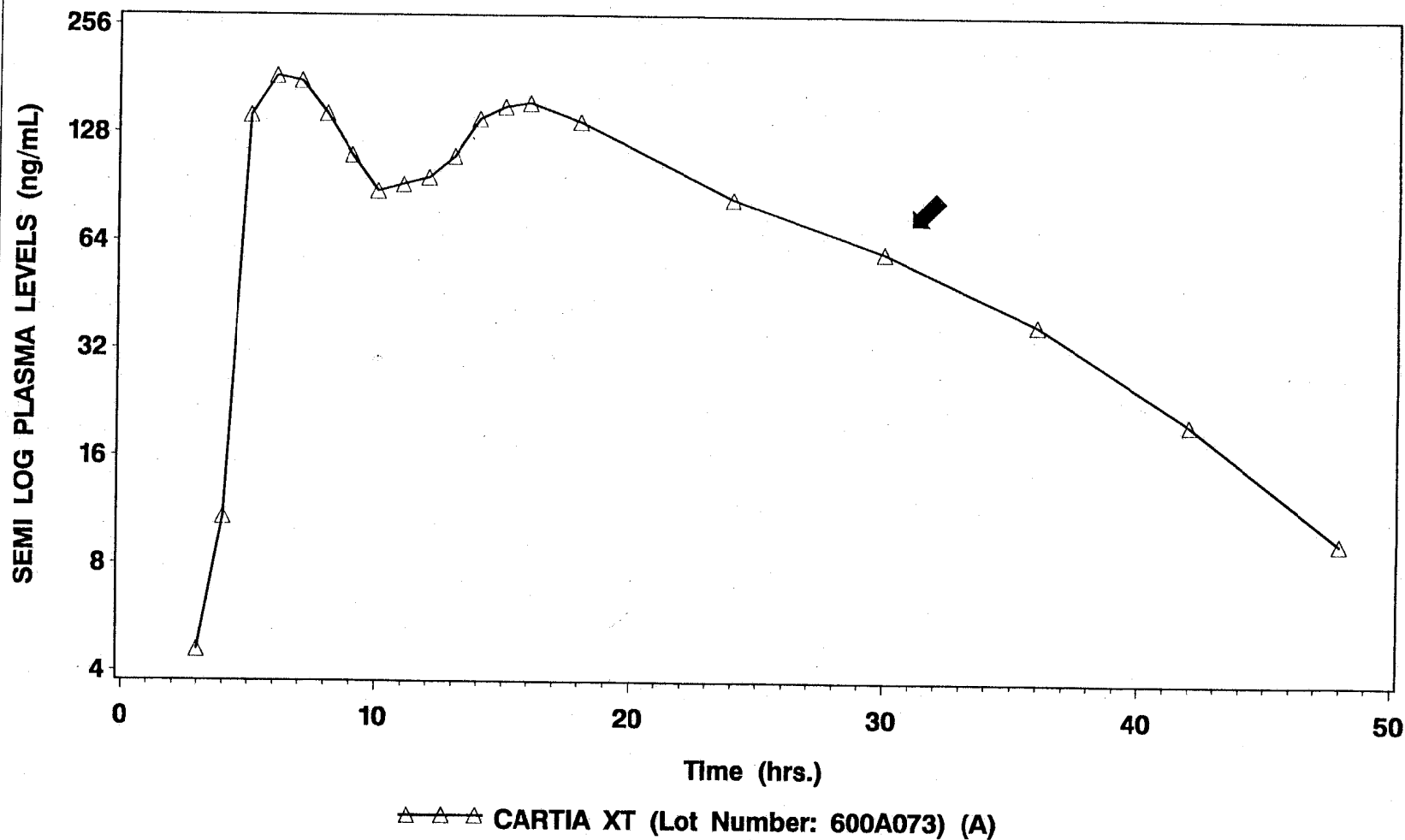


FIGURE 1.55

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 28

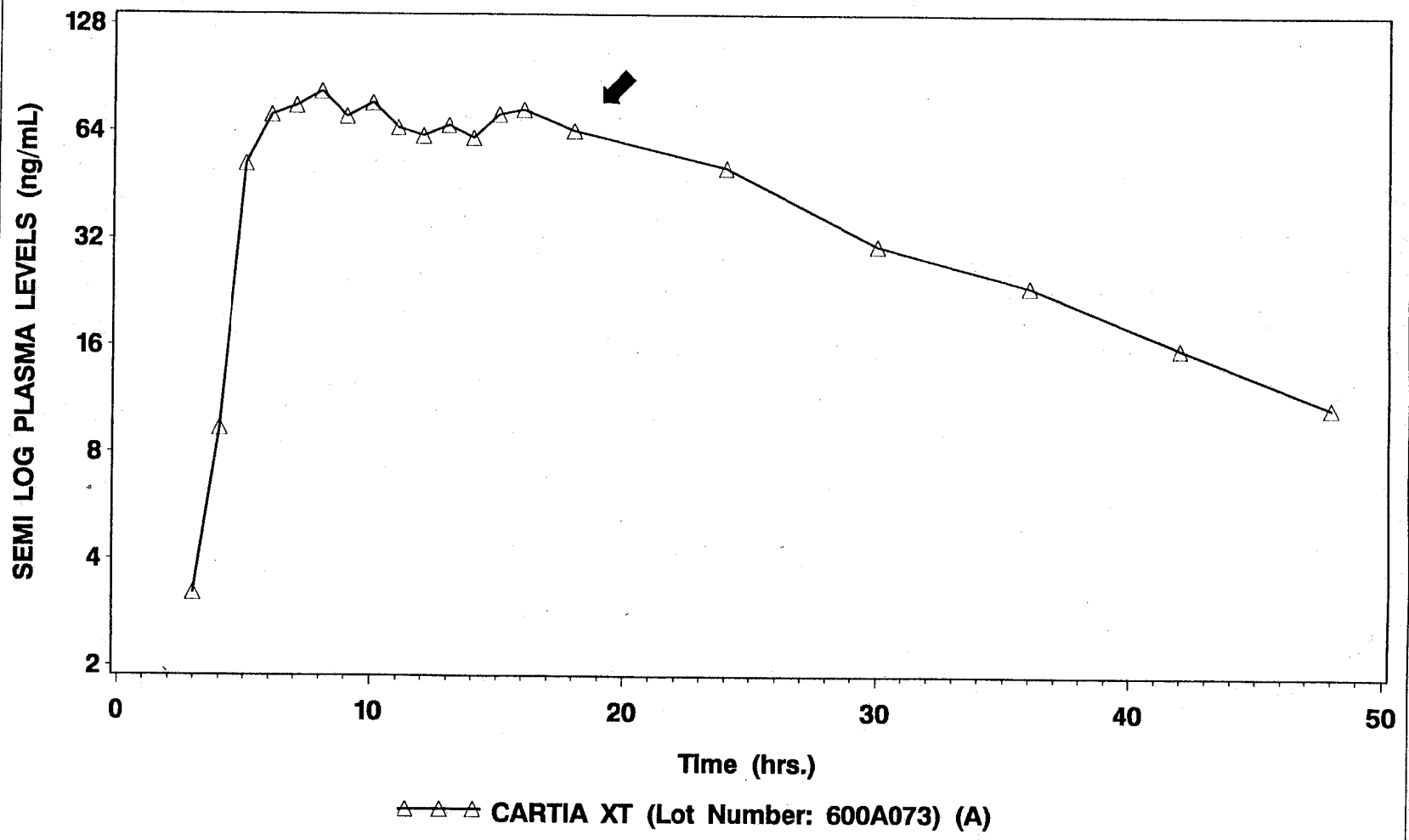


FIGURE 1.56

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=01

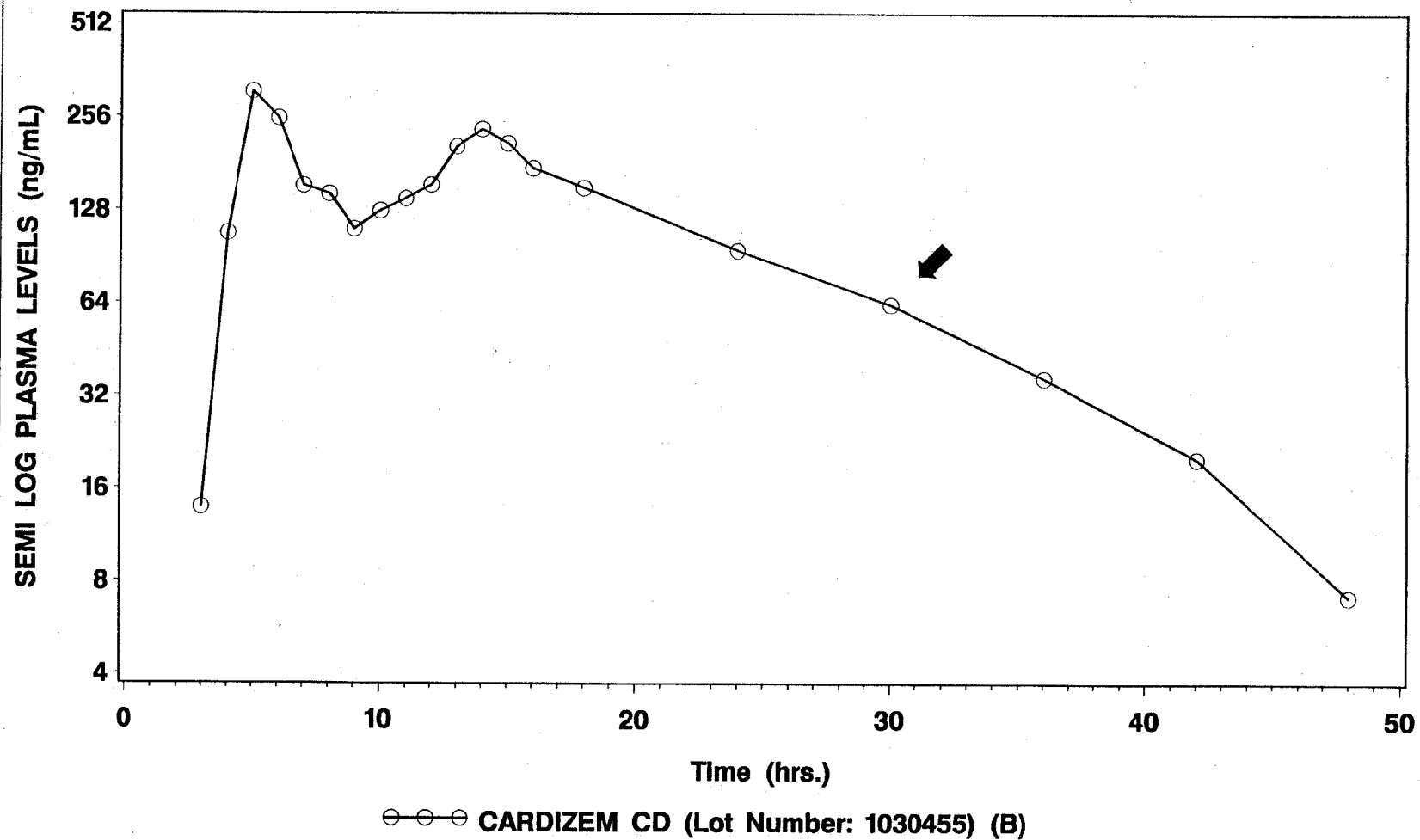


FIGURE 1.57

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 03

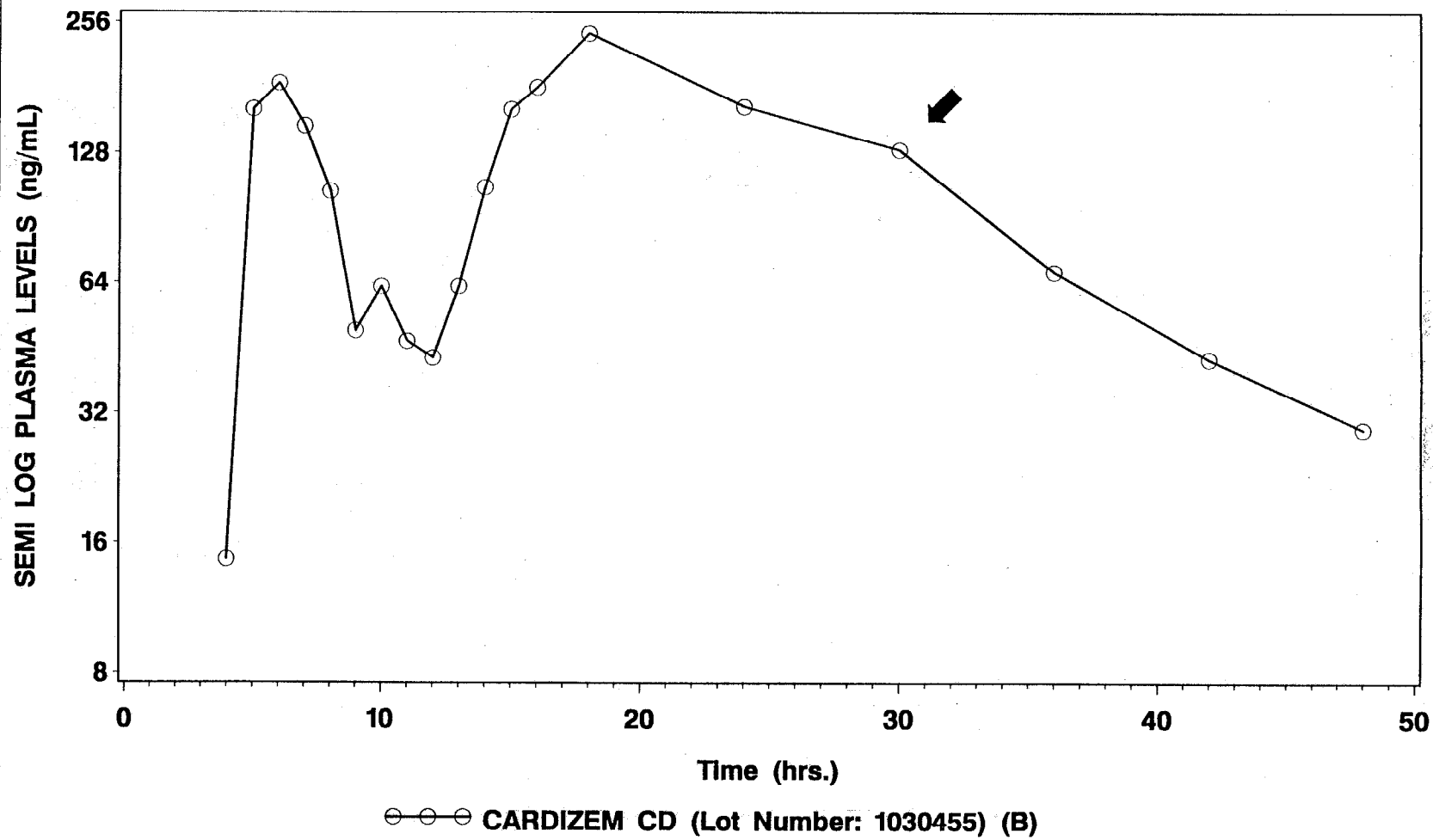


FIGURE 1.58

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 05

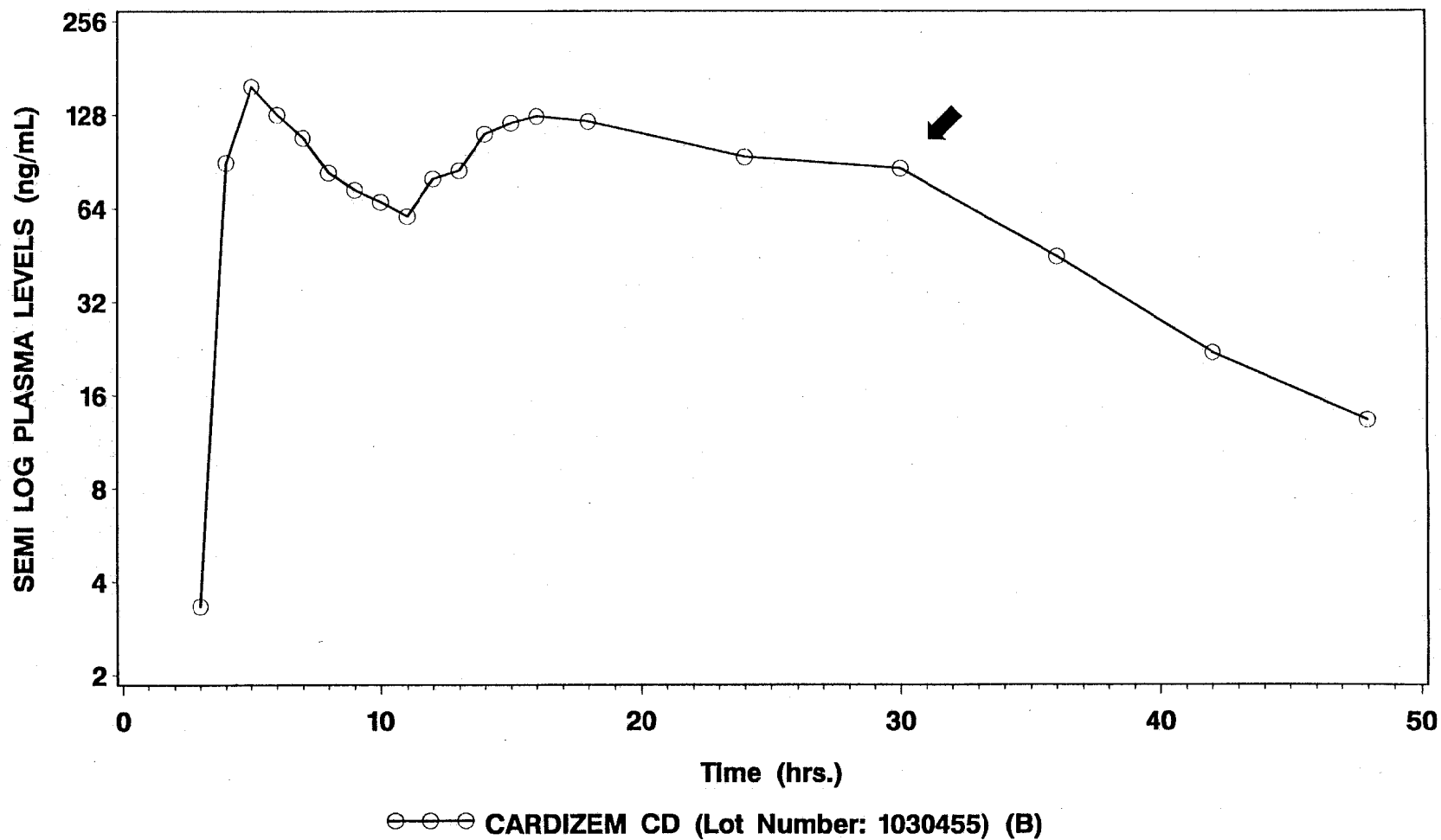


FIGURE 1.60

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 06

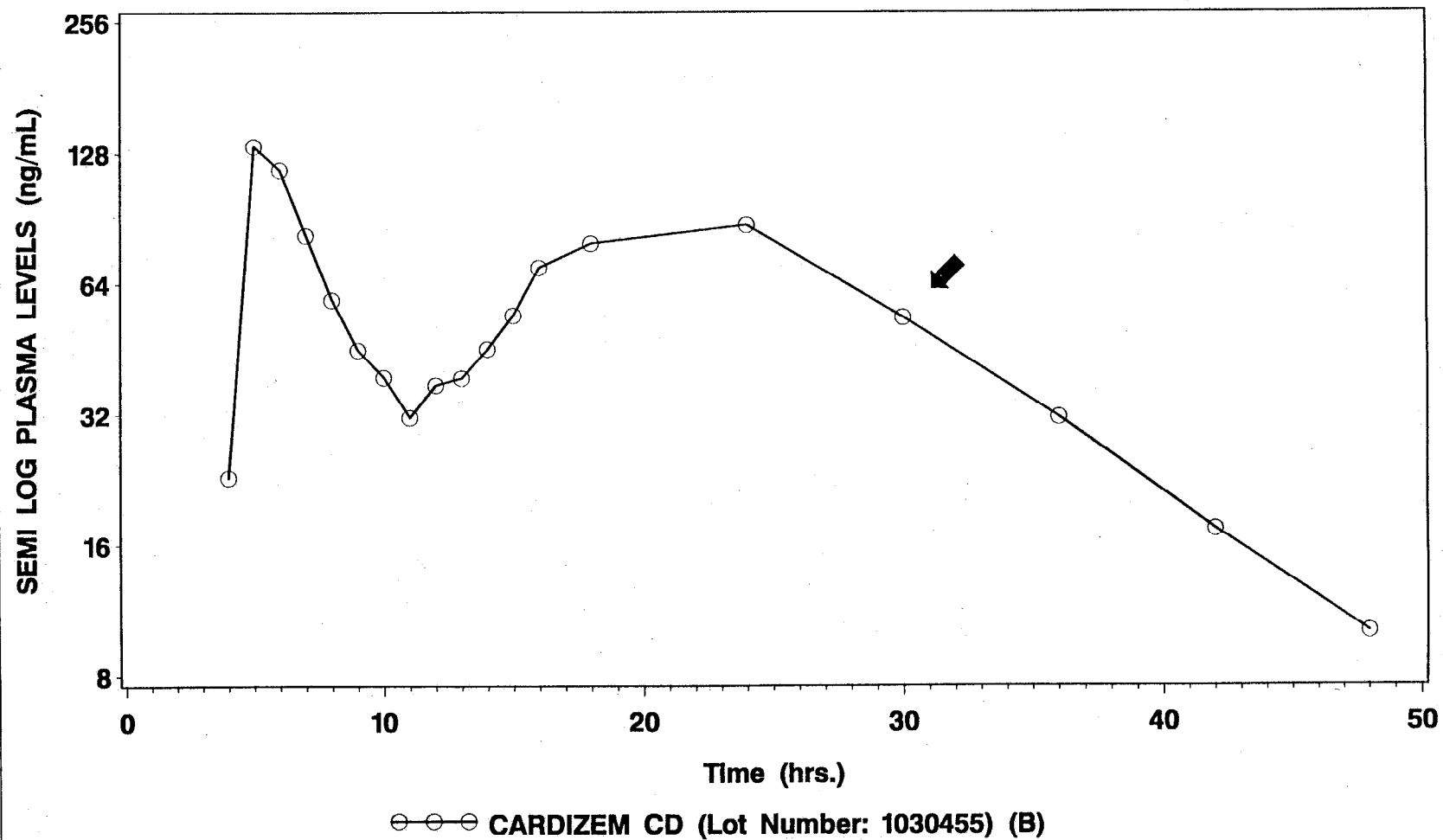


FIGURE 1.61

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 07

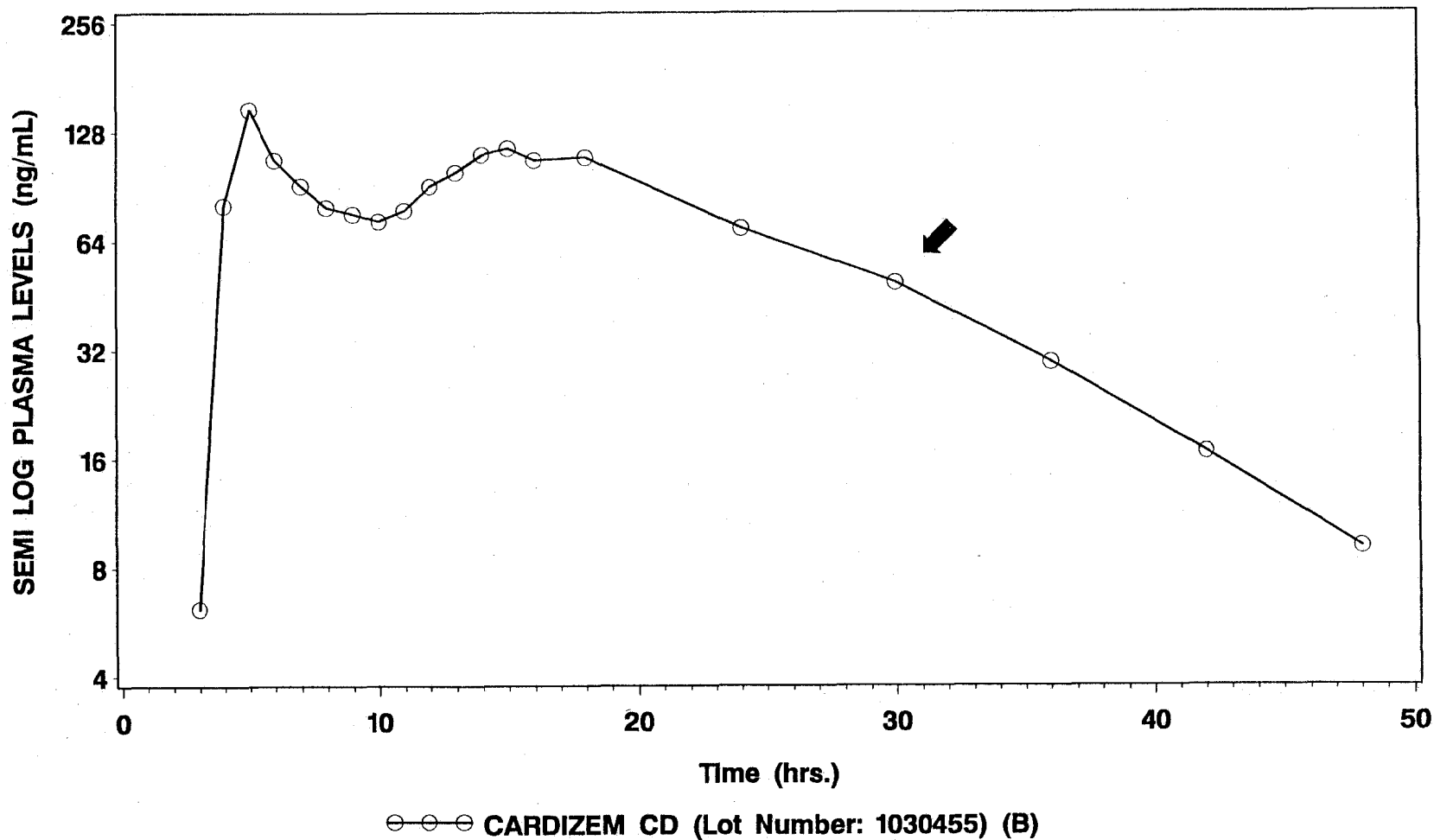


FIGURE 1.62

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 08

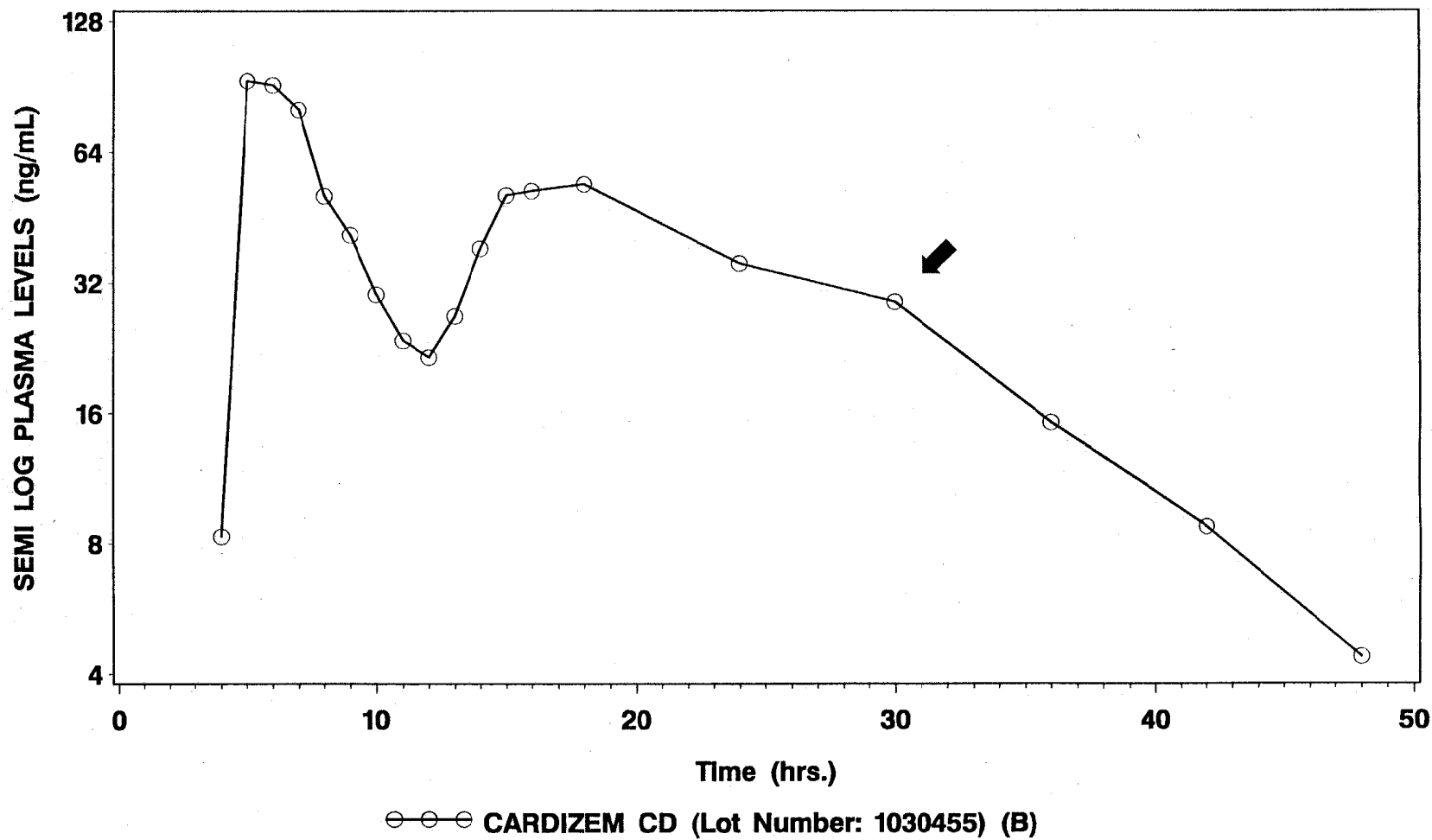


FIGURE 1.63

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 09

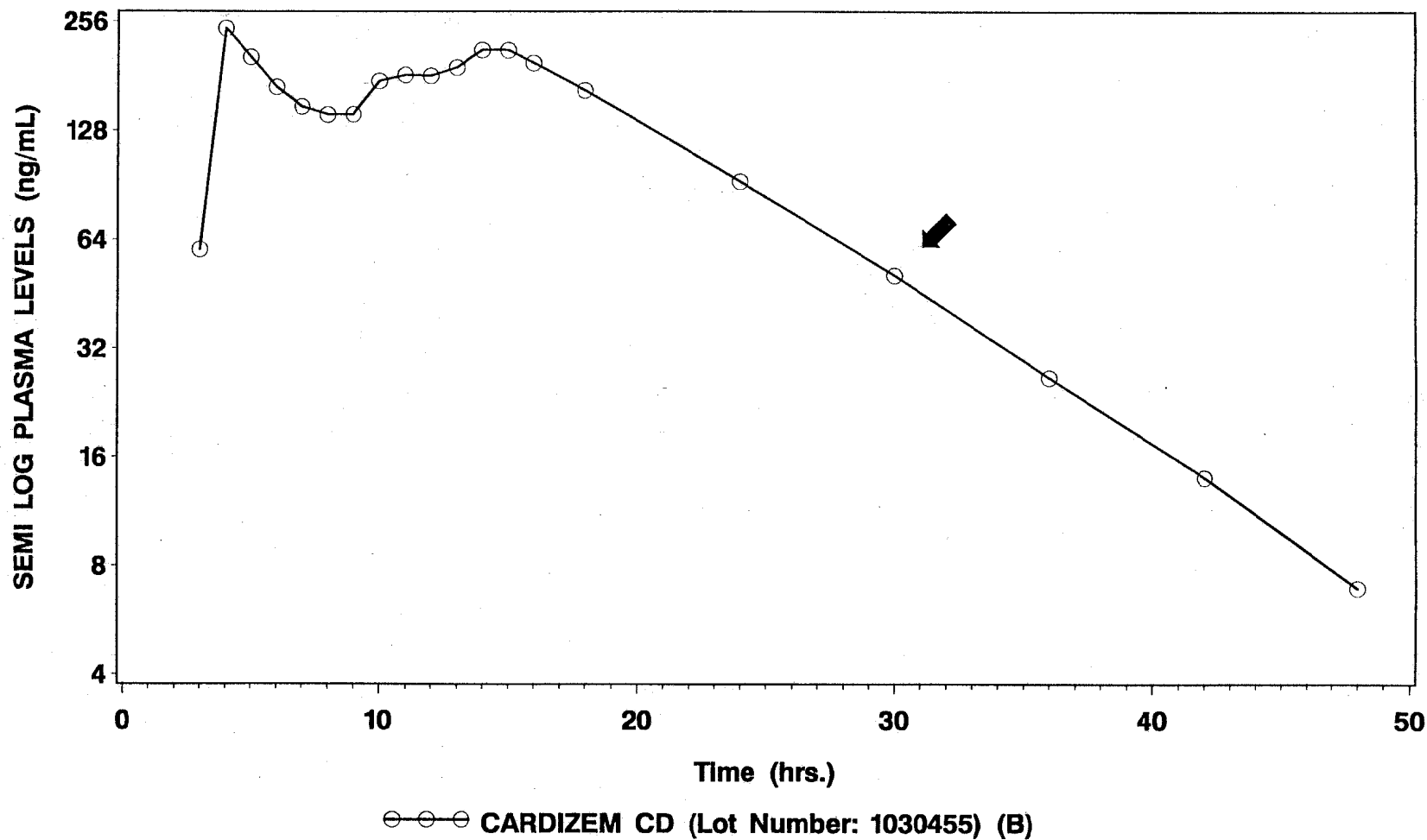


FIGURE 1.64

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 10

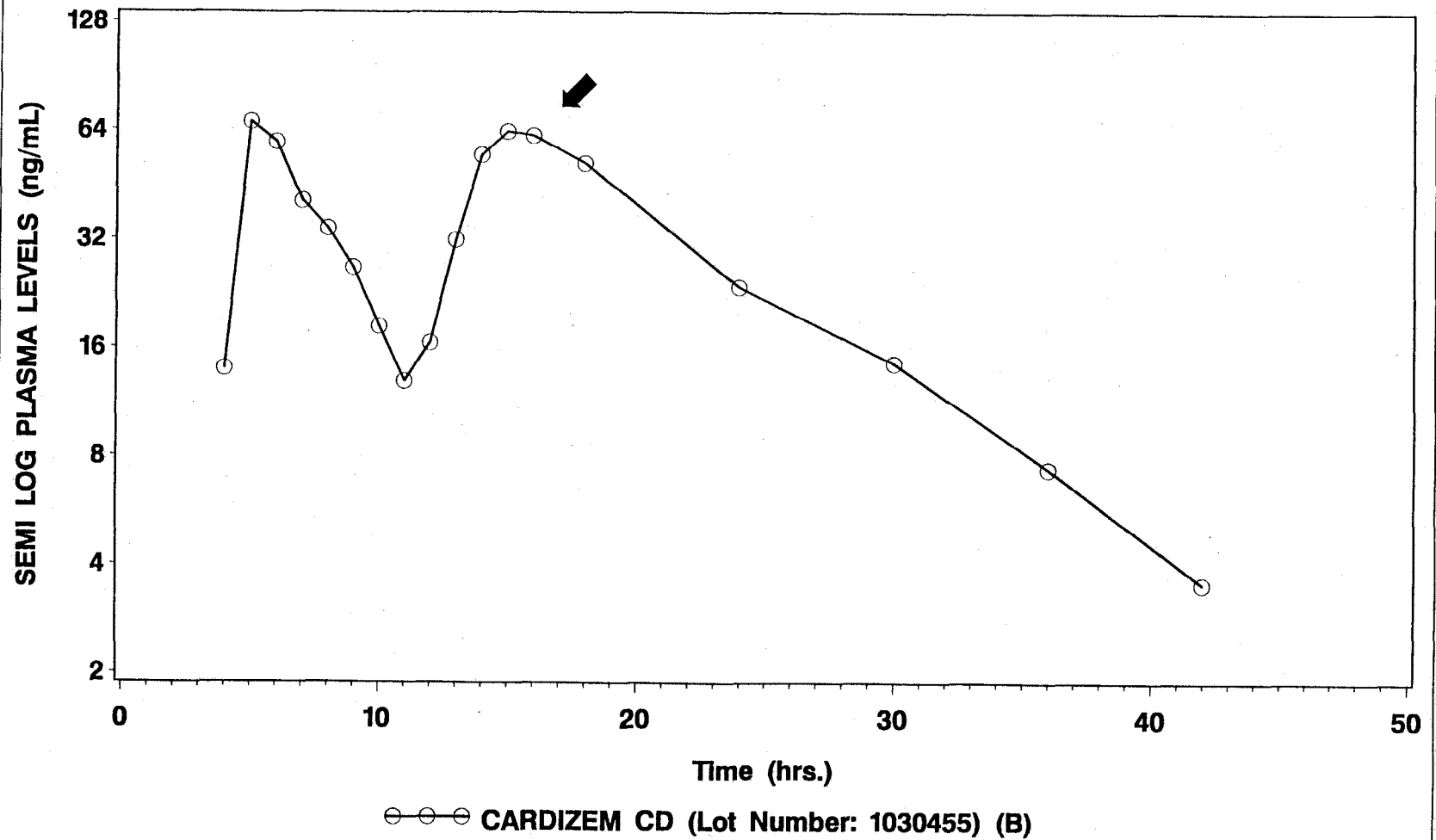


FIGURE 1.65

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 11

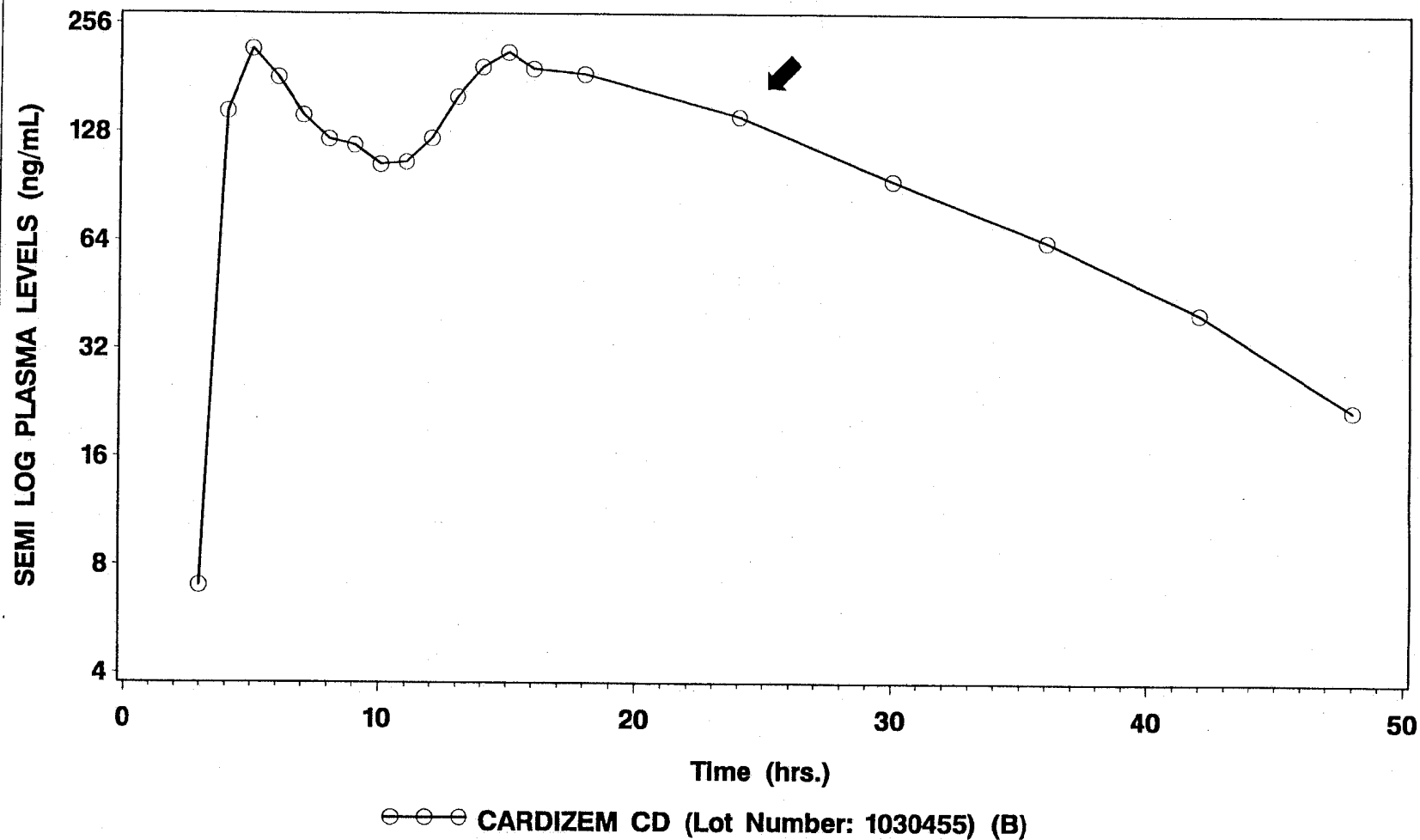


FIGURE 1.66

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=12

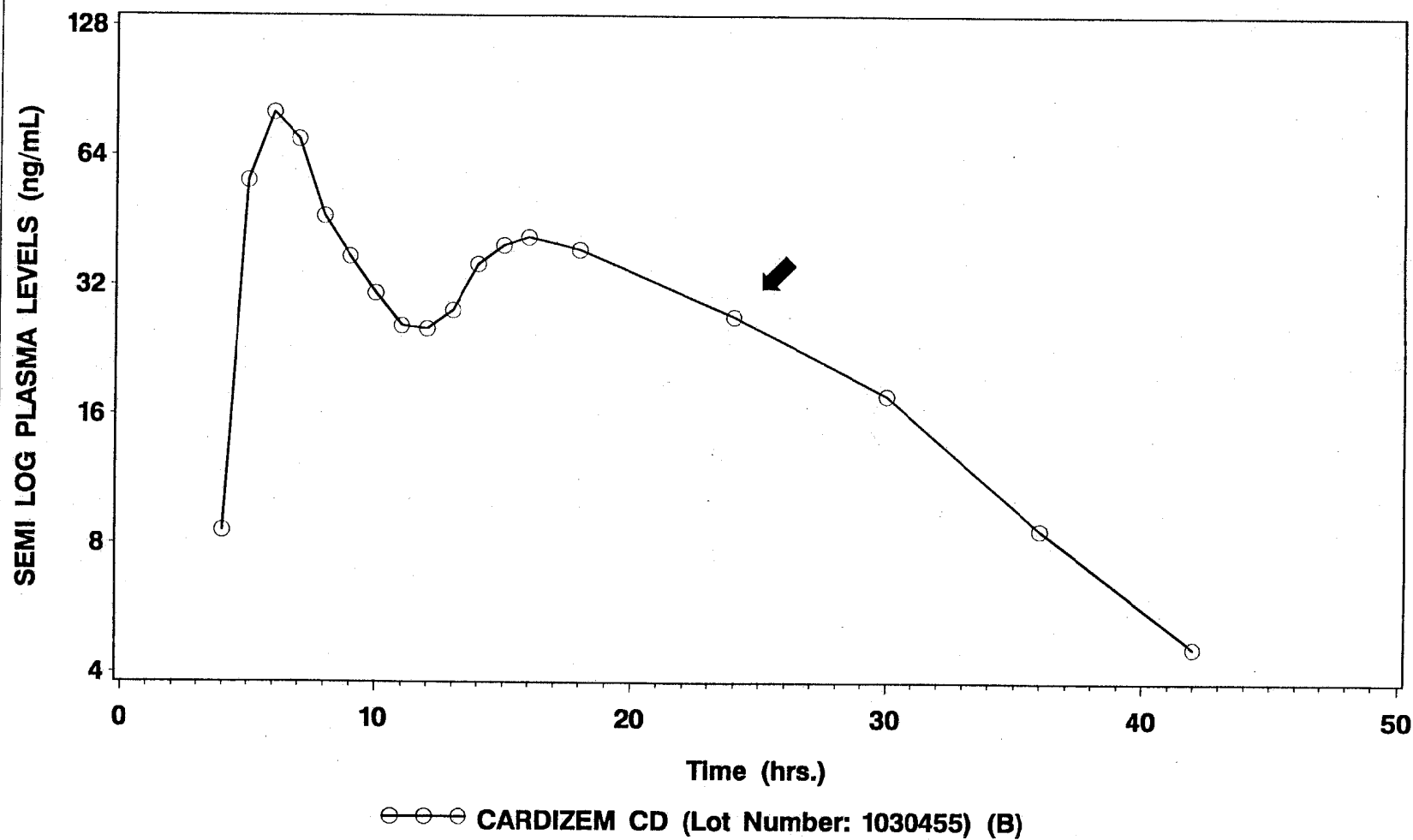


FIGURE 1.67

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 13

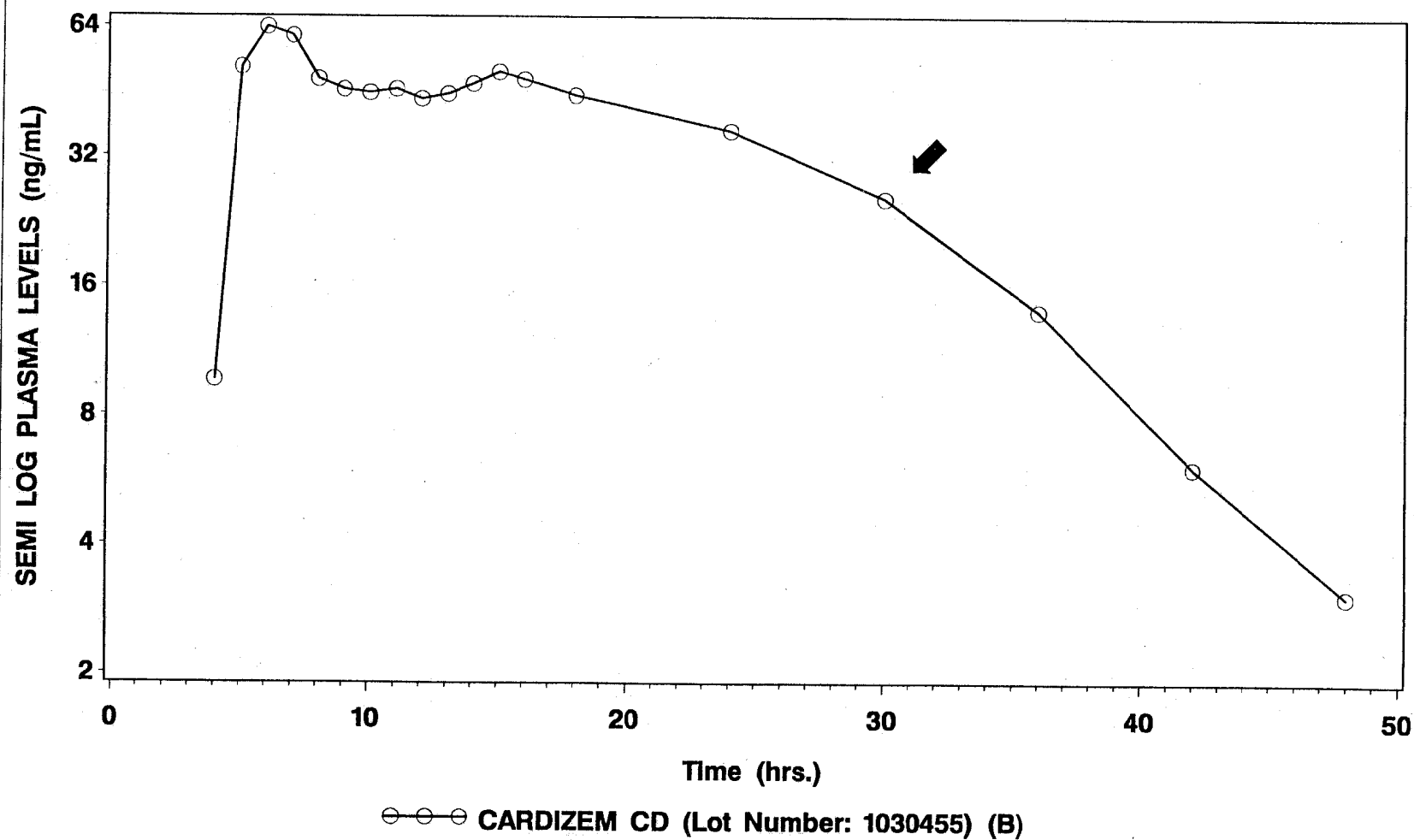


FIGURE 1.68

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=14

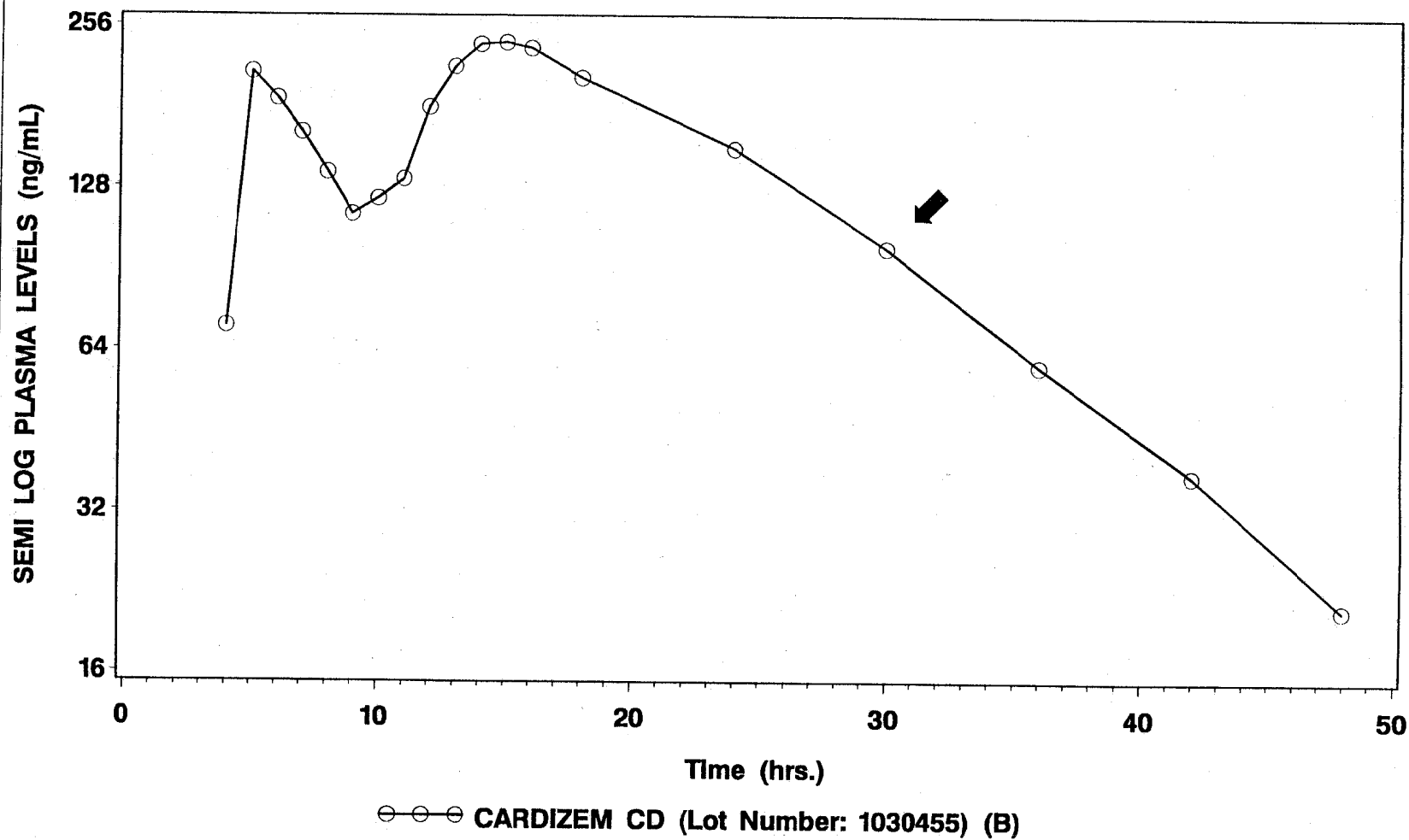


FIGURE 1.69

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 15

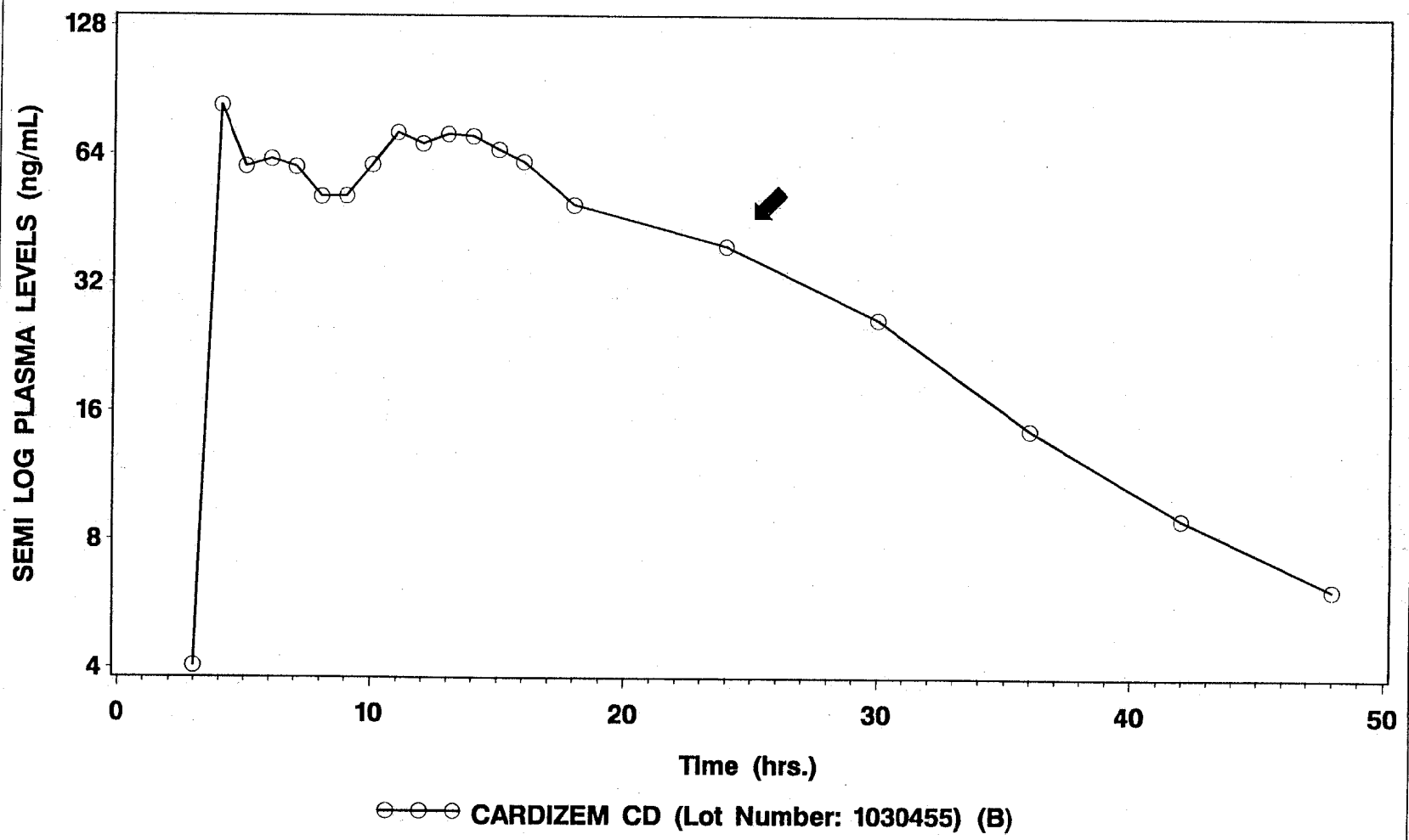


FIGURE 1.70

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=16

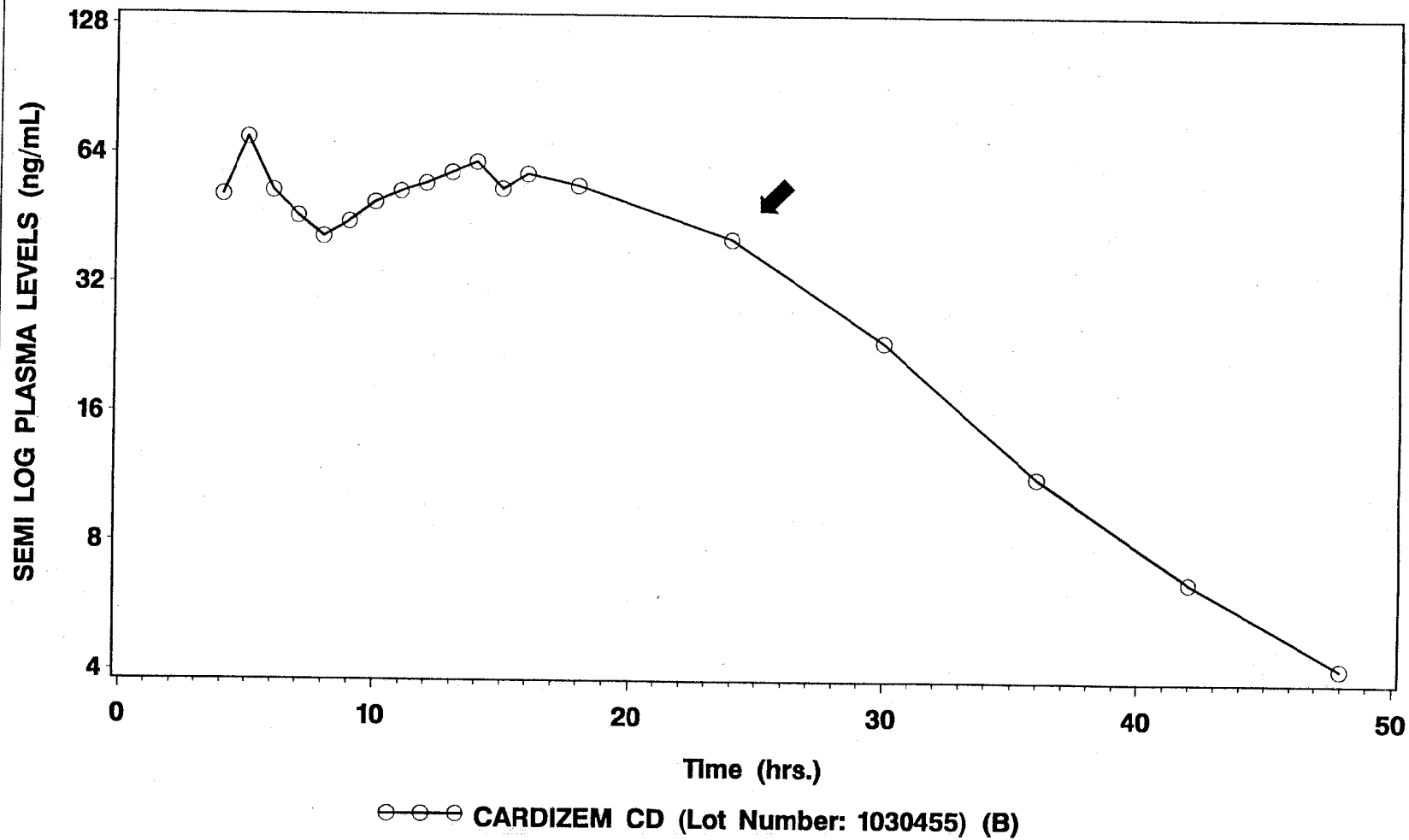


FIGURE 1.71

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 17

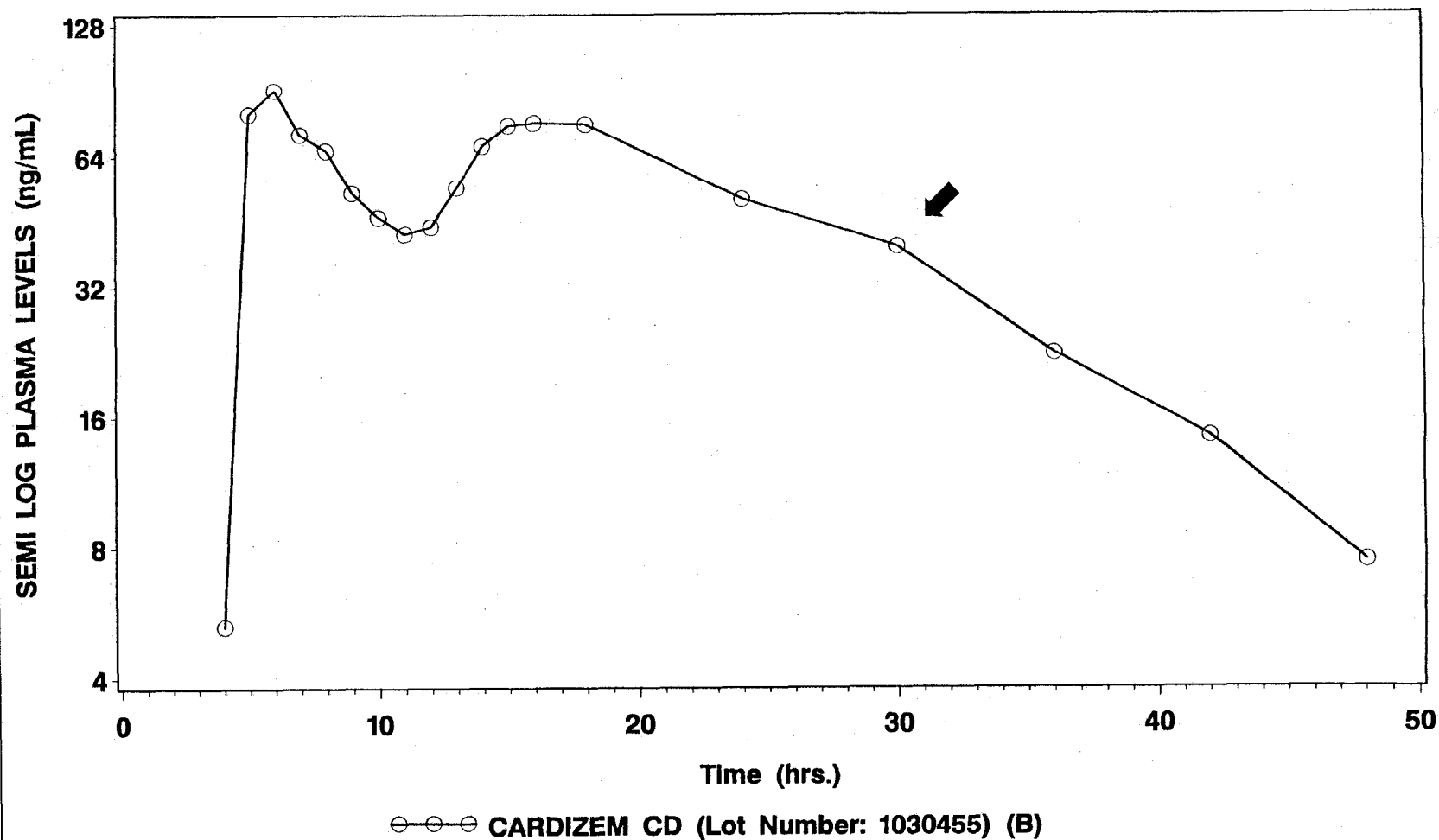


FIGURE 1.72

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 18

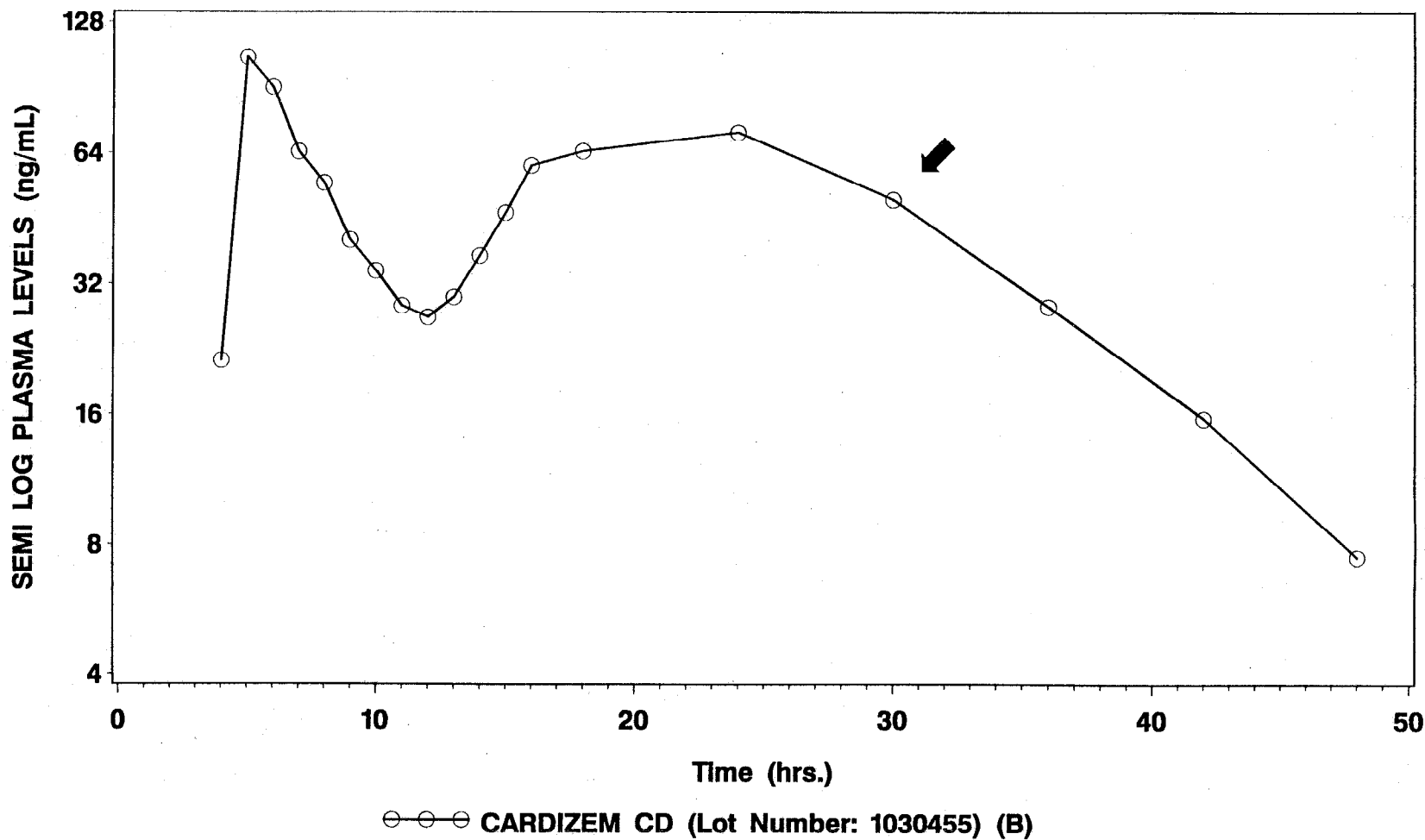
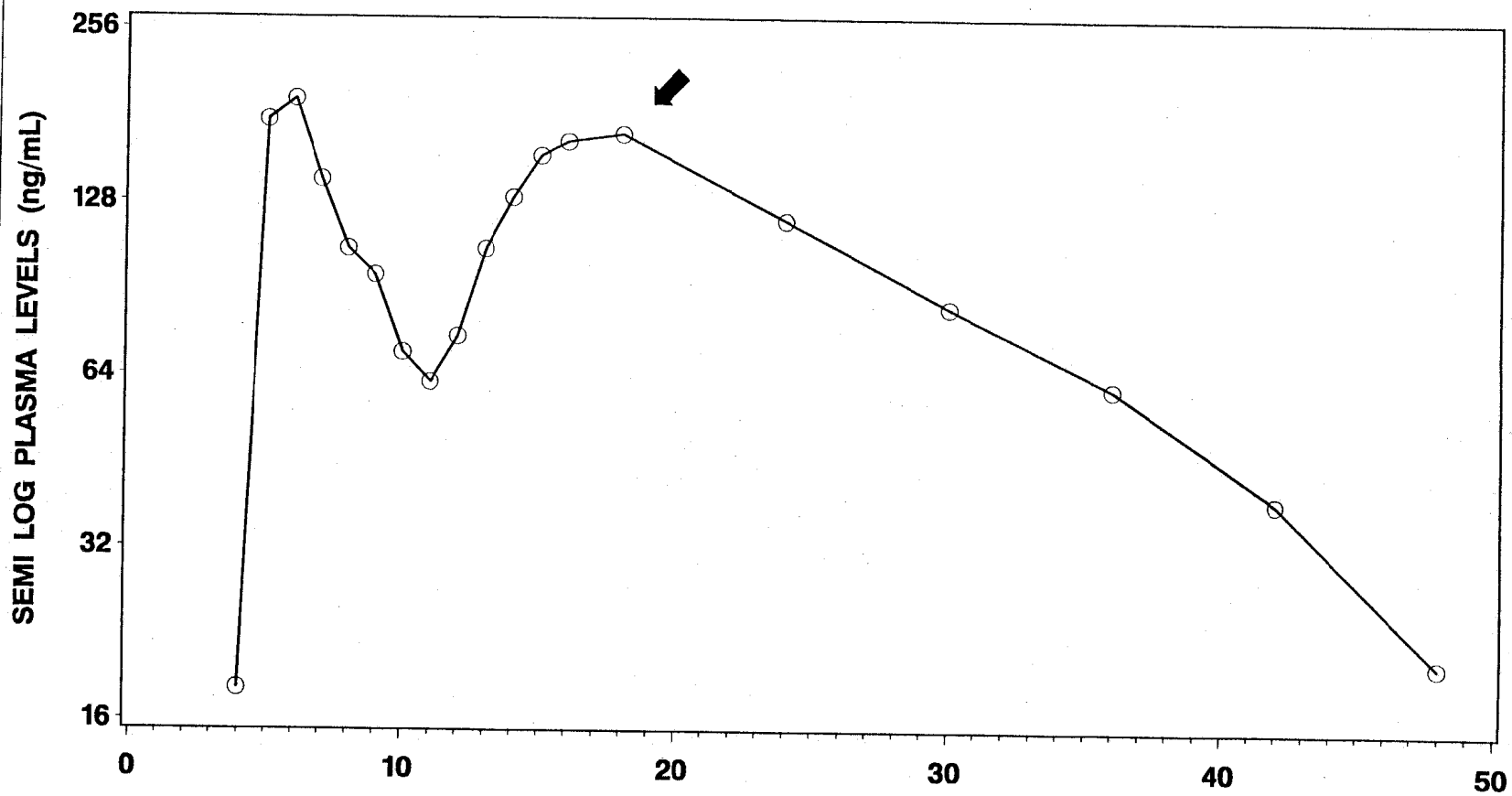


FIGURE 1.73

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=19



○—○—○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 1.74

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 20

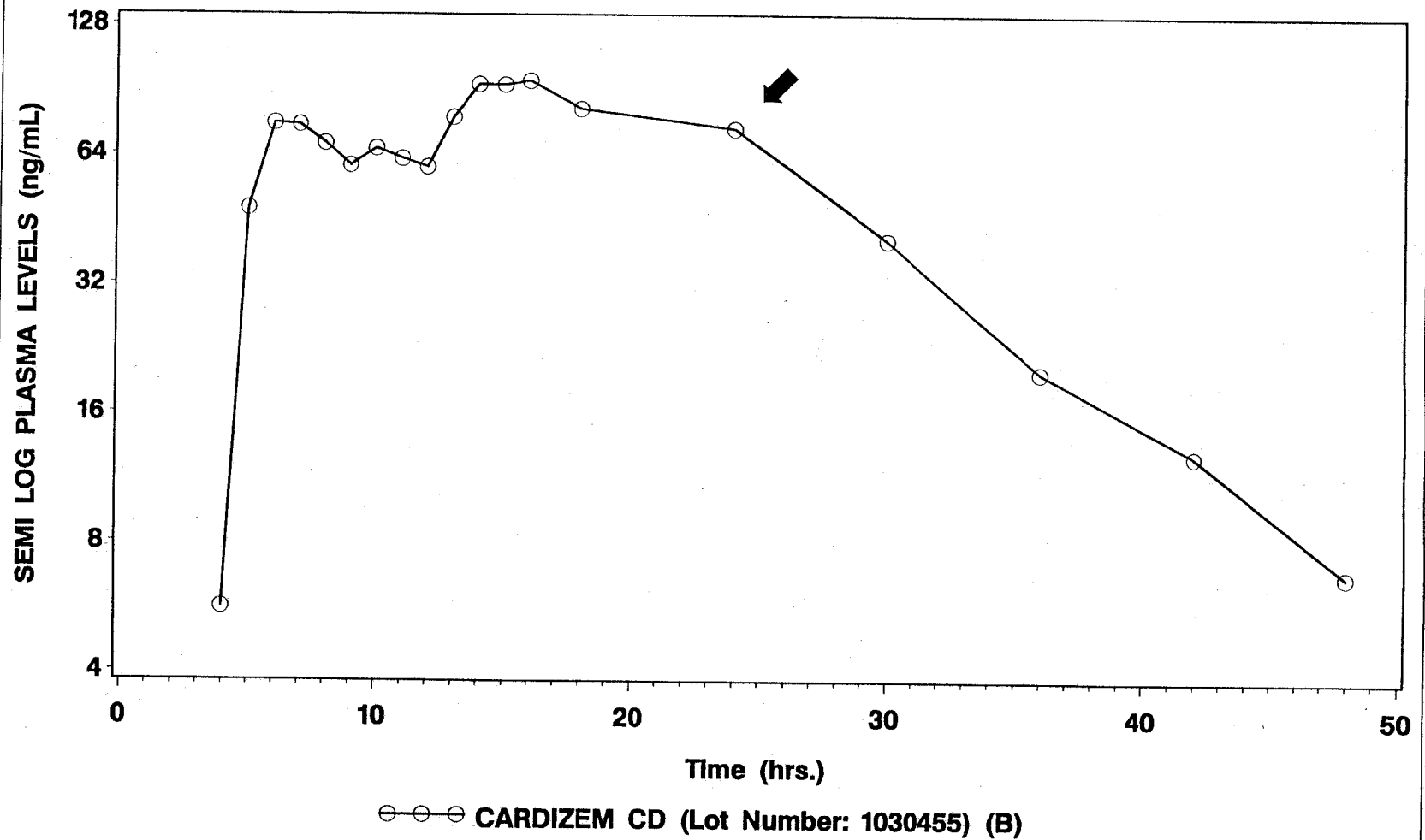


FIGURE 1.75

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 21

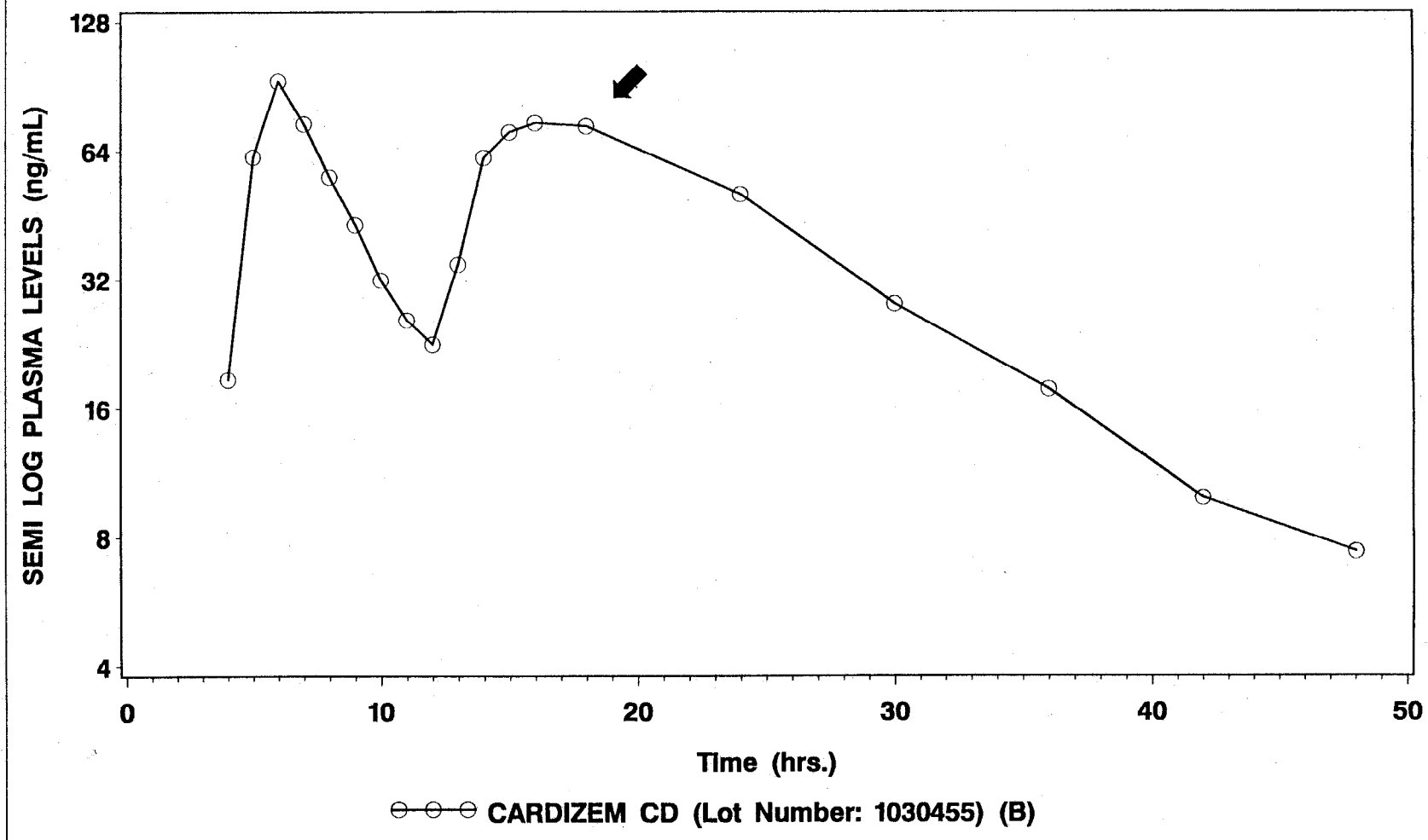


FIGURE 1.76

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 22

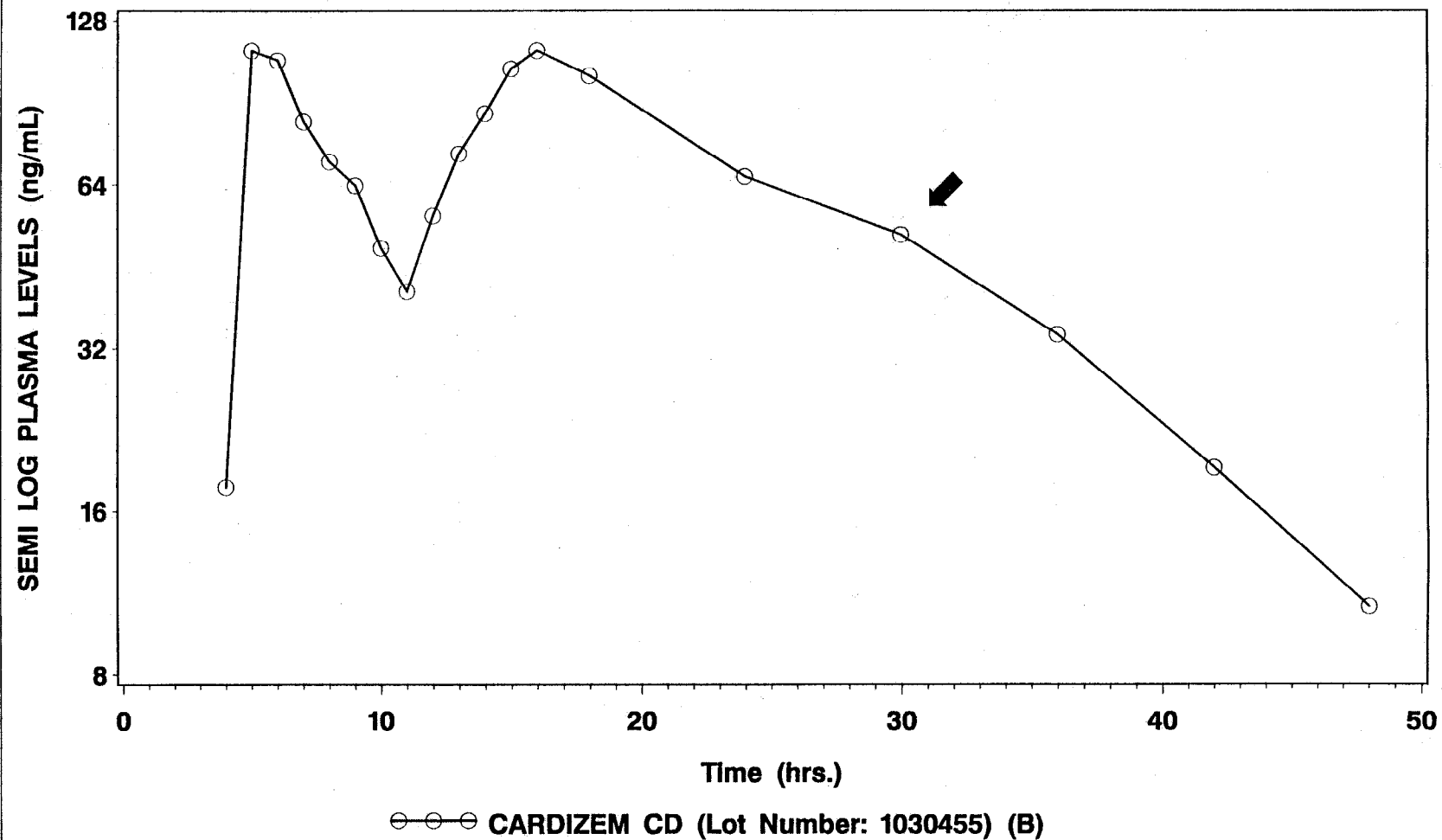


FIGURE 1.77

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 23

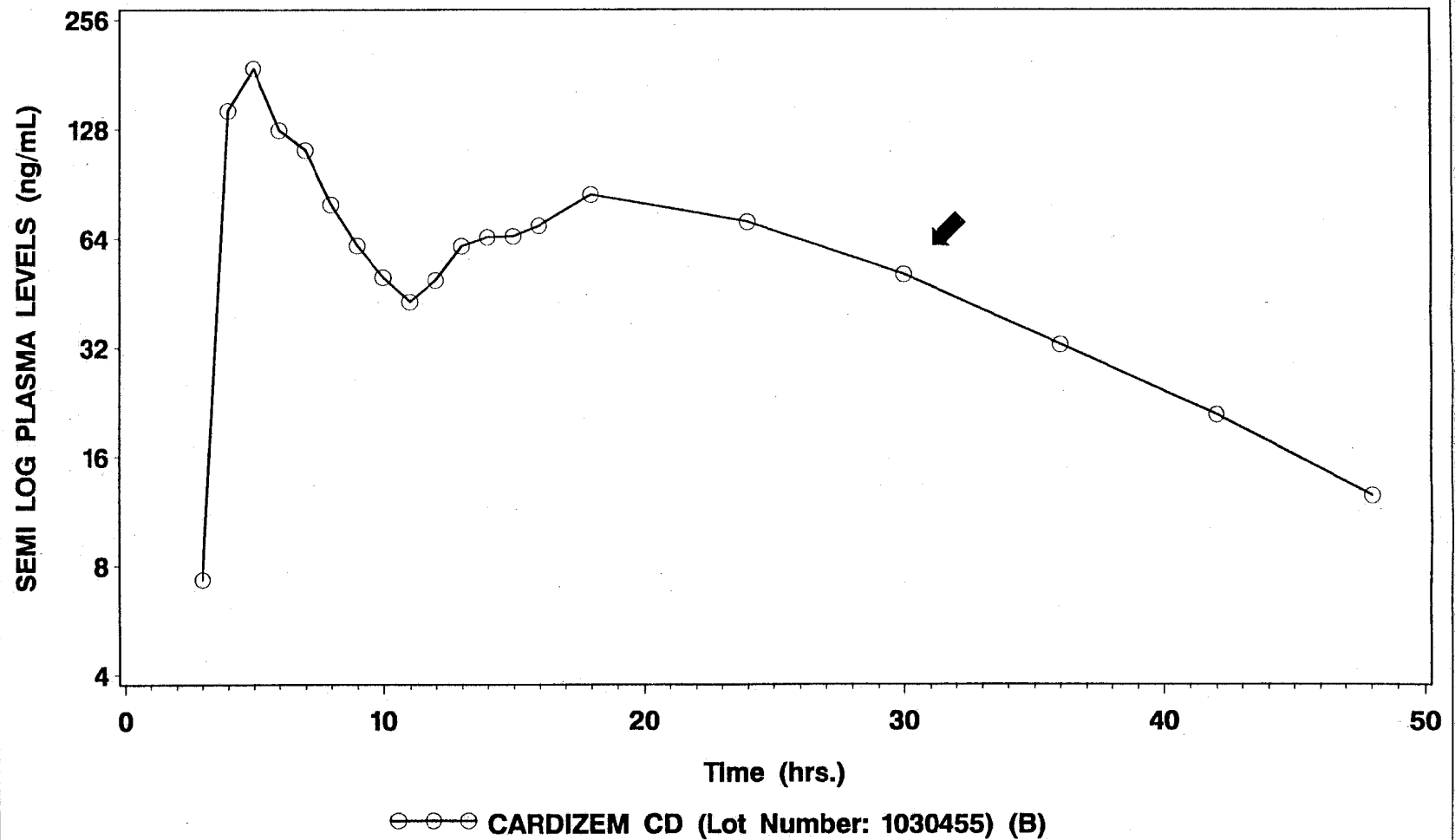


FIGURE 1.78

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 24

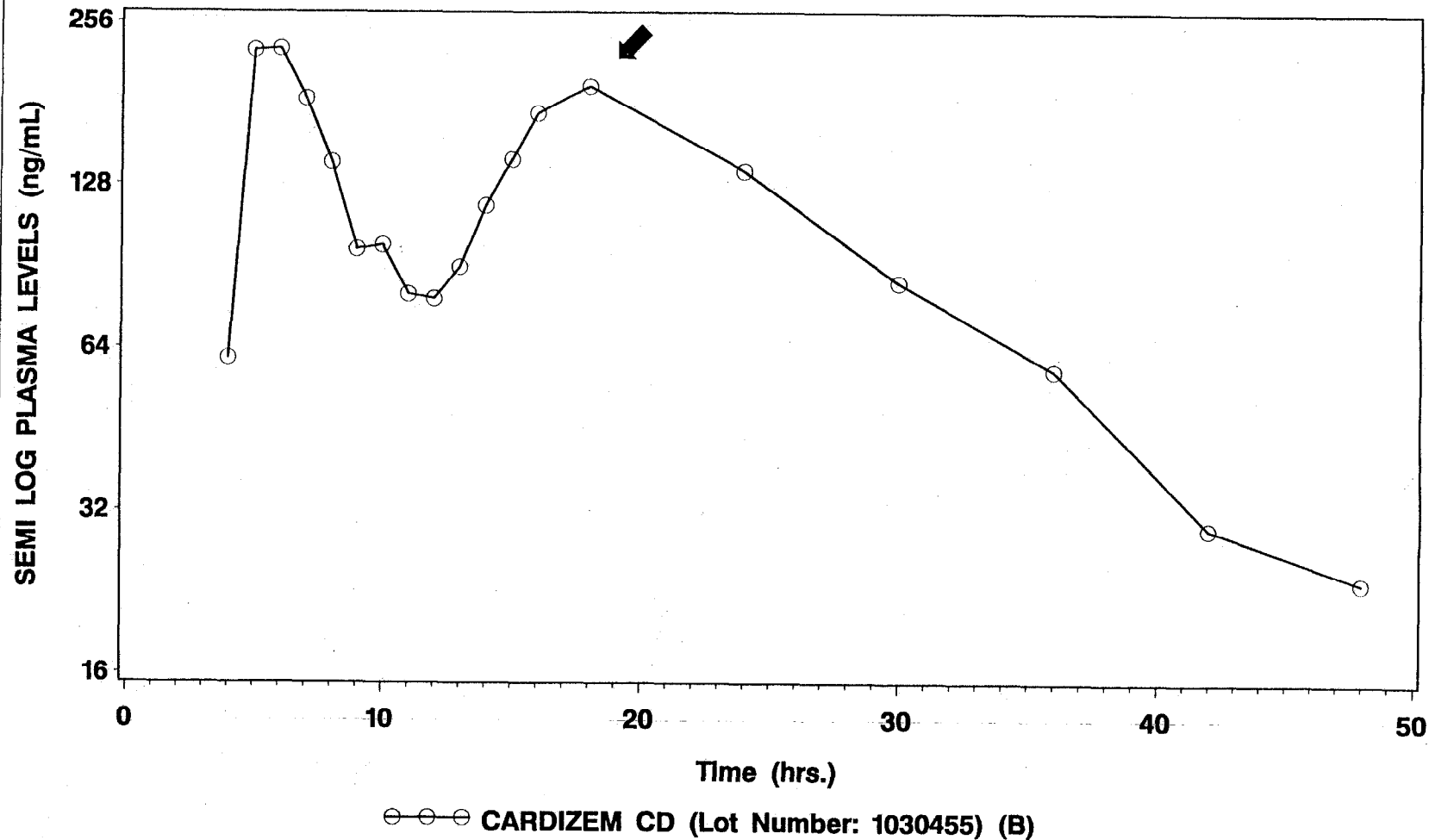


FIGURE 1.79

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 25

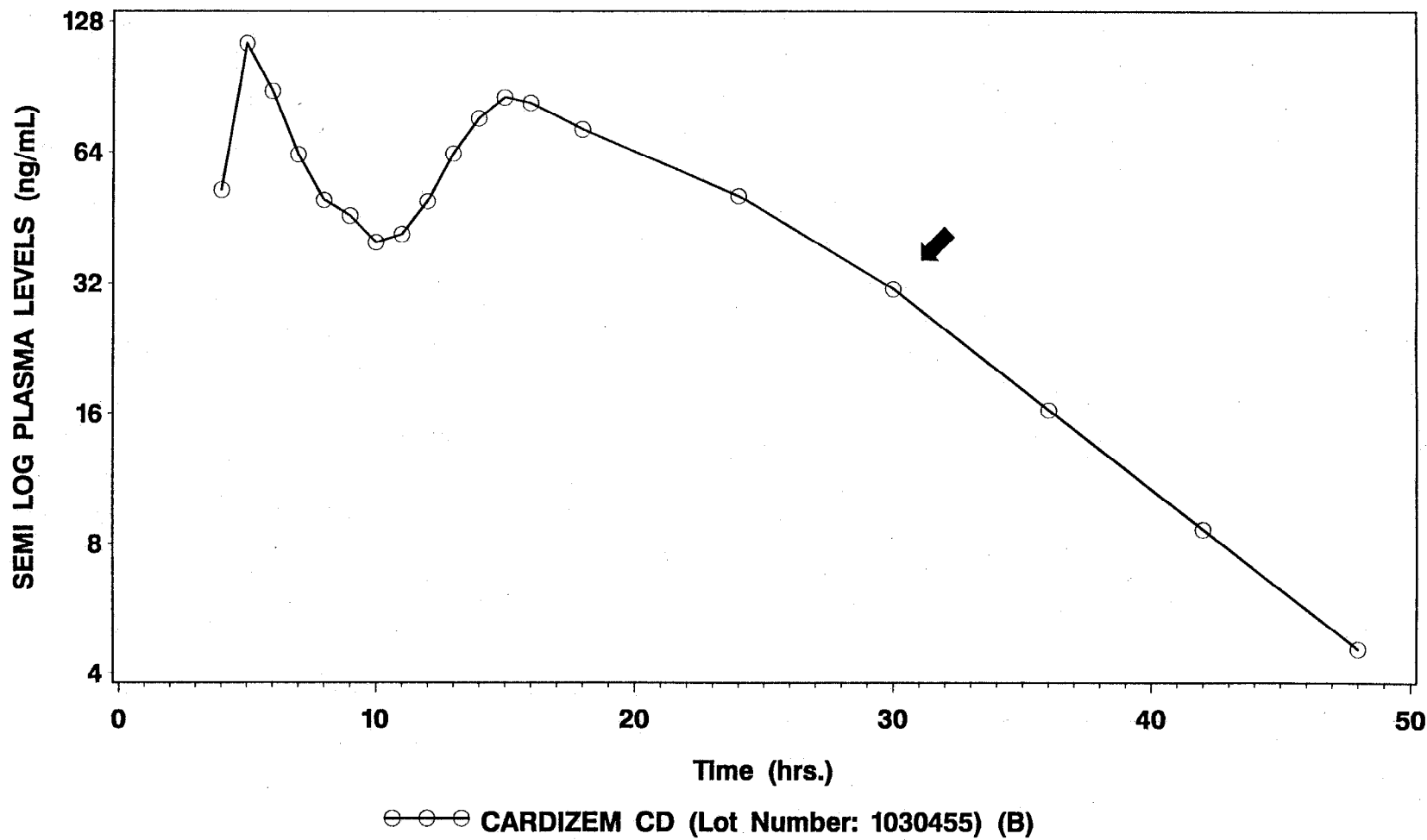


FIGURE 1.80

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 26

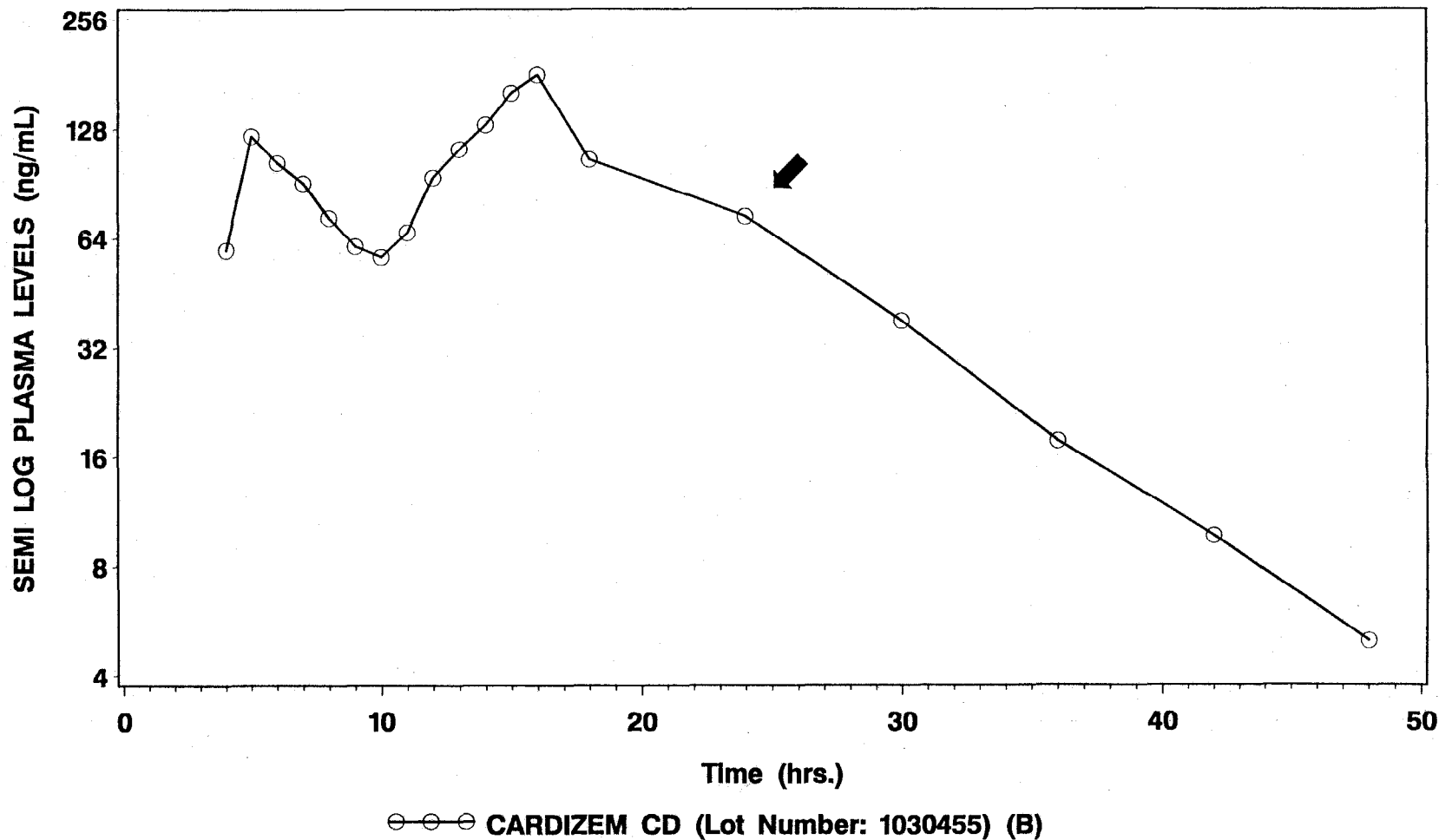


FIGURE 1.81

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 27

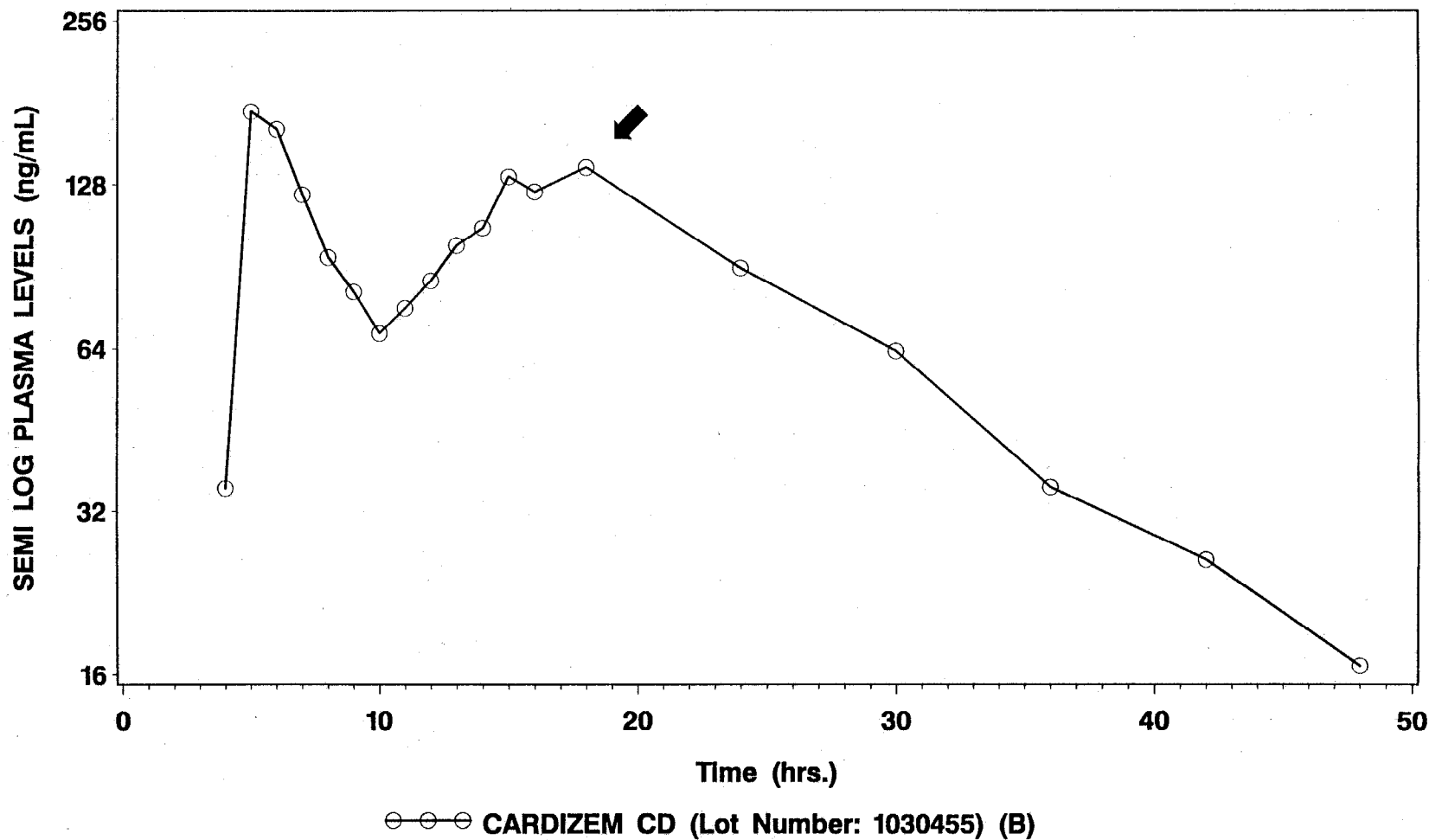


FIGURE 1.82

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 28

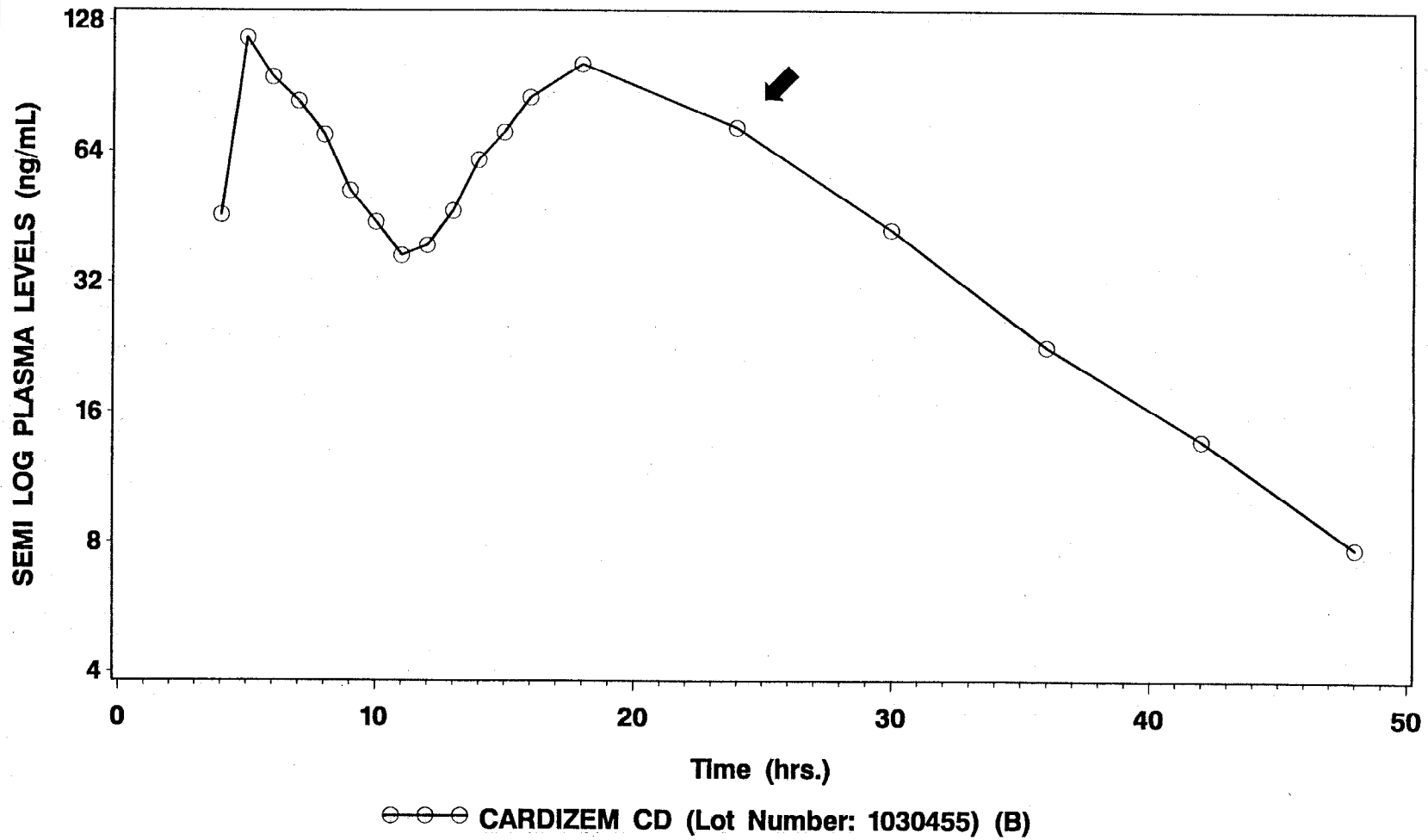


FIGURE 1.83

**Distribution of Difference of AUC (0-t) Between Formulations for DILTIAZEM
(STUDY # 2443)**

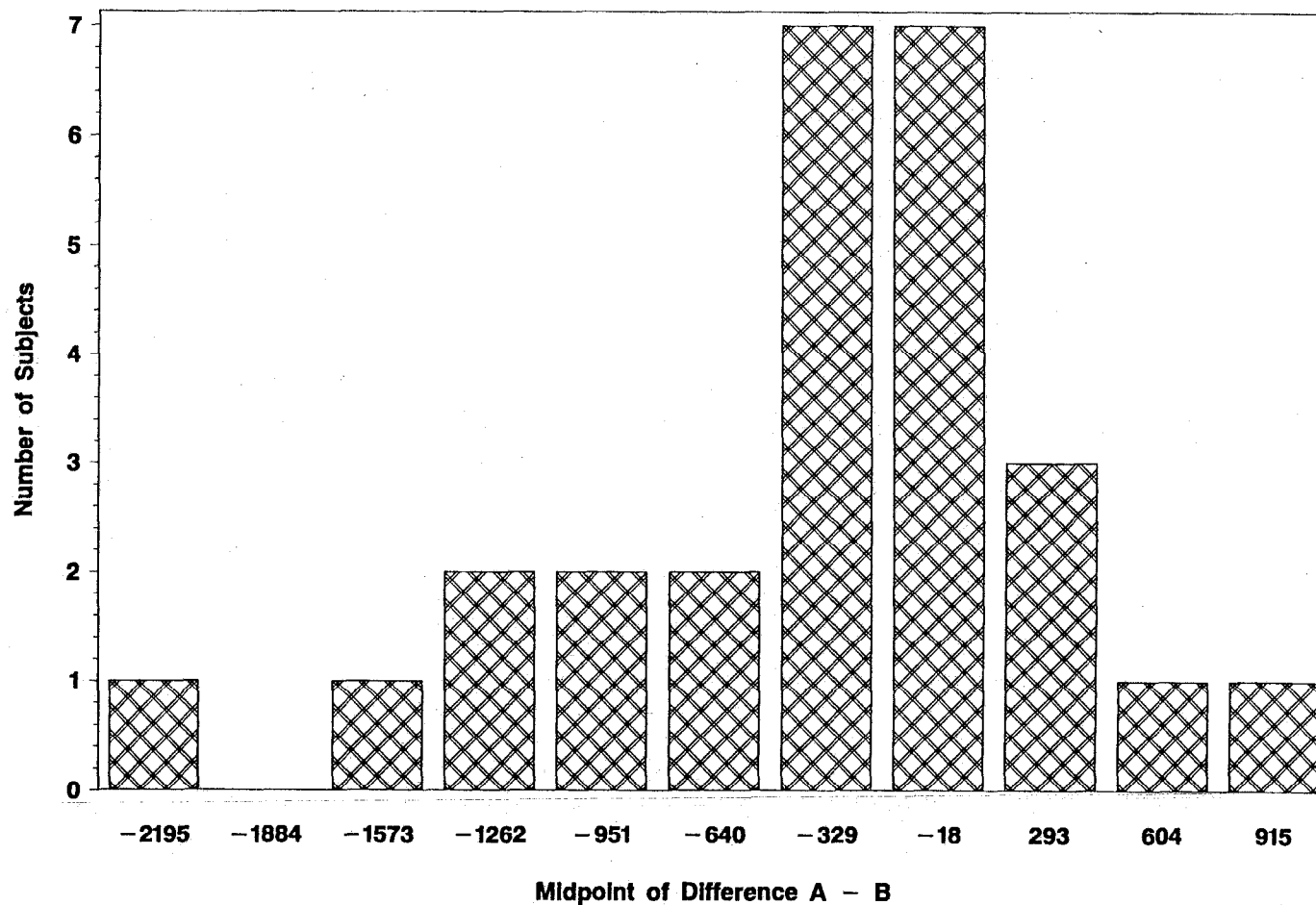


FIGURE 1.A

**Distribution of Ratio of AUC (0-t) Between Formulations for DILTIAZEM
(STUDY # 2443)**

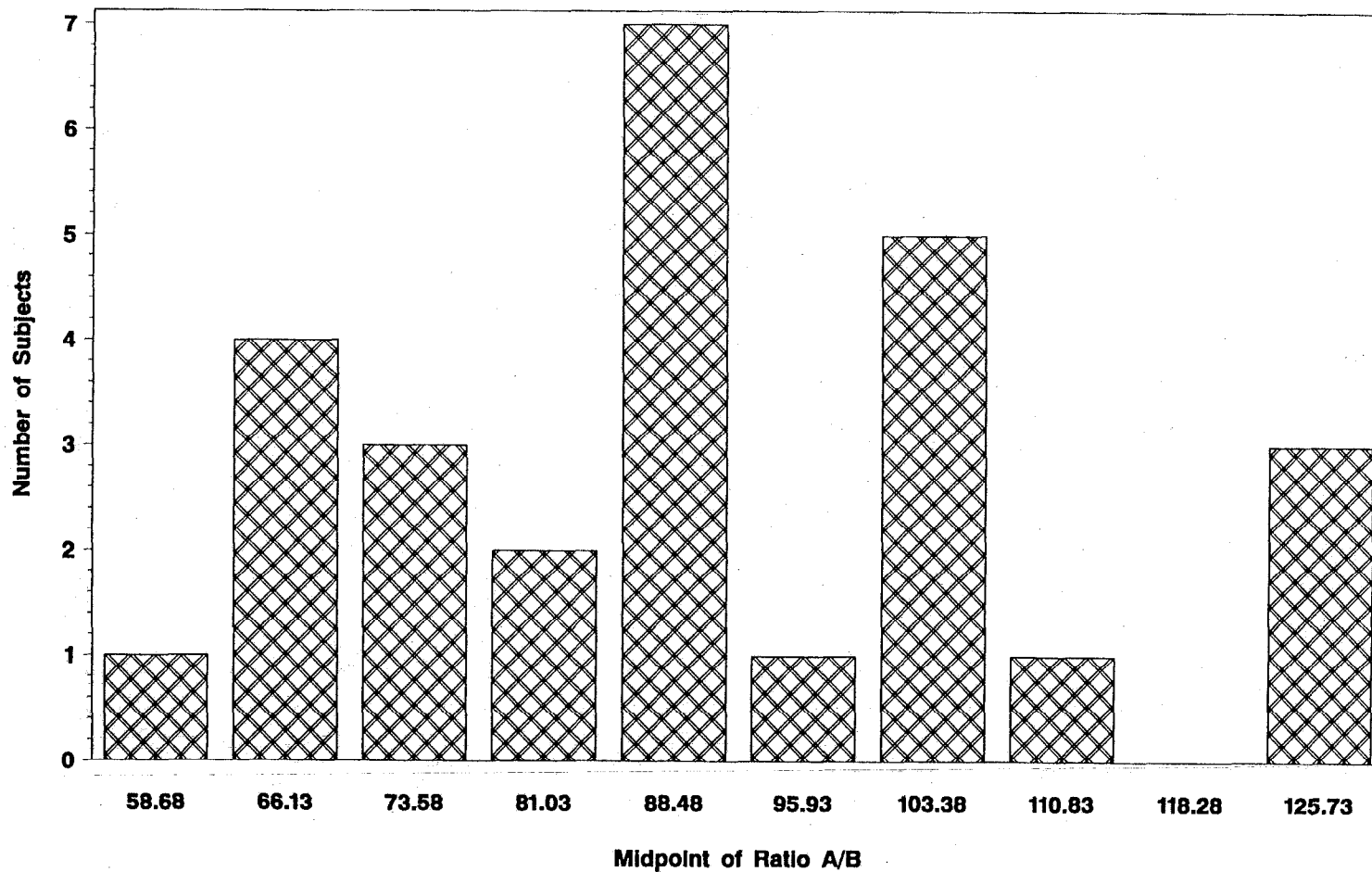


FIGURE 1.B

**Distribution of Difference of AUC (0 – inf) Between Formulations for DILTIAZEM
(STUDY # 2443)**

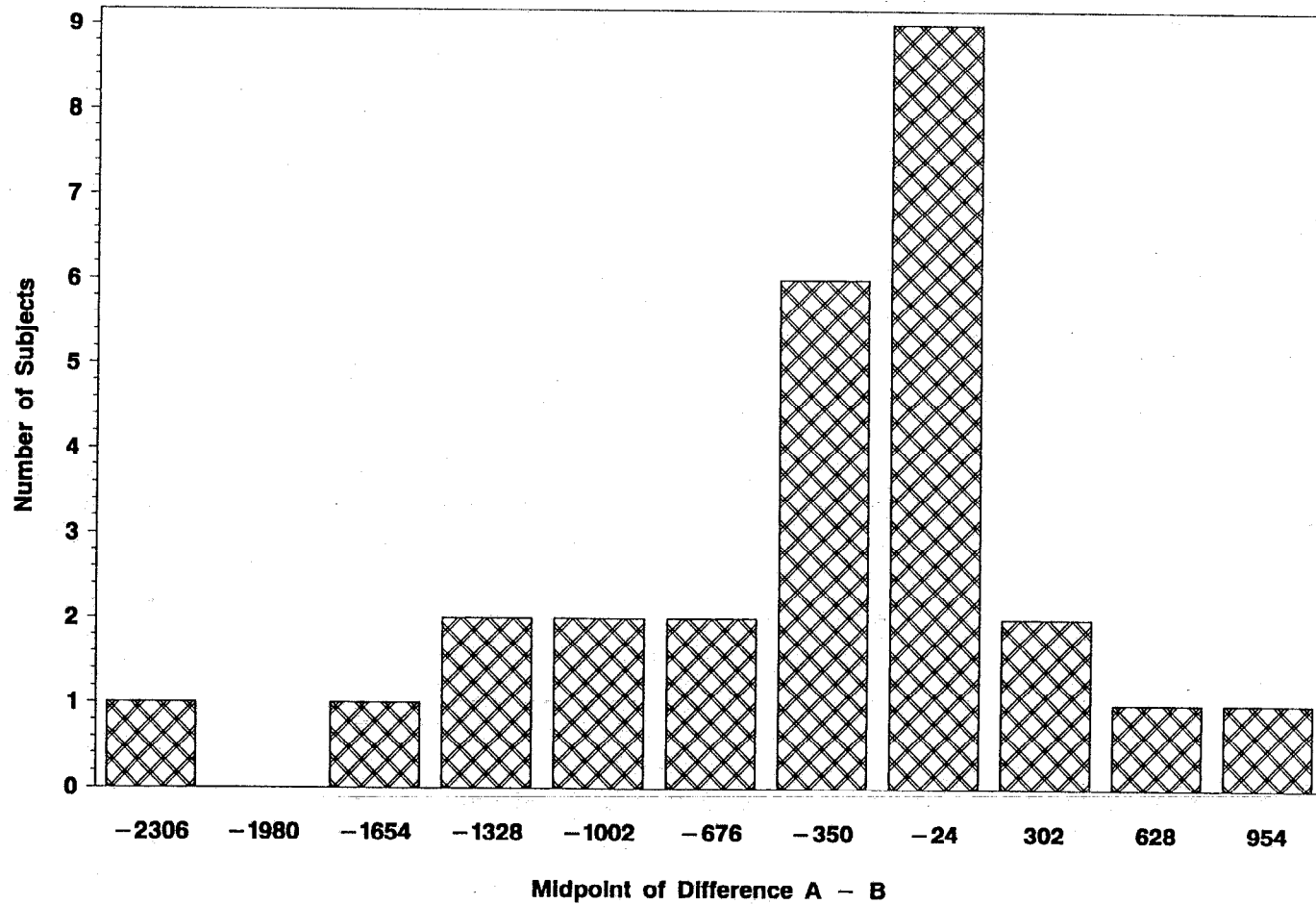


FIGURE 1.C

**Distribution of Ratio of AUC (0 – inf) Between Formulations for DILTIAZEM
(STUDY # 2443)**

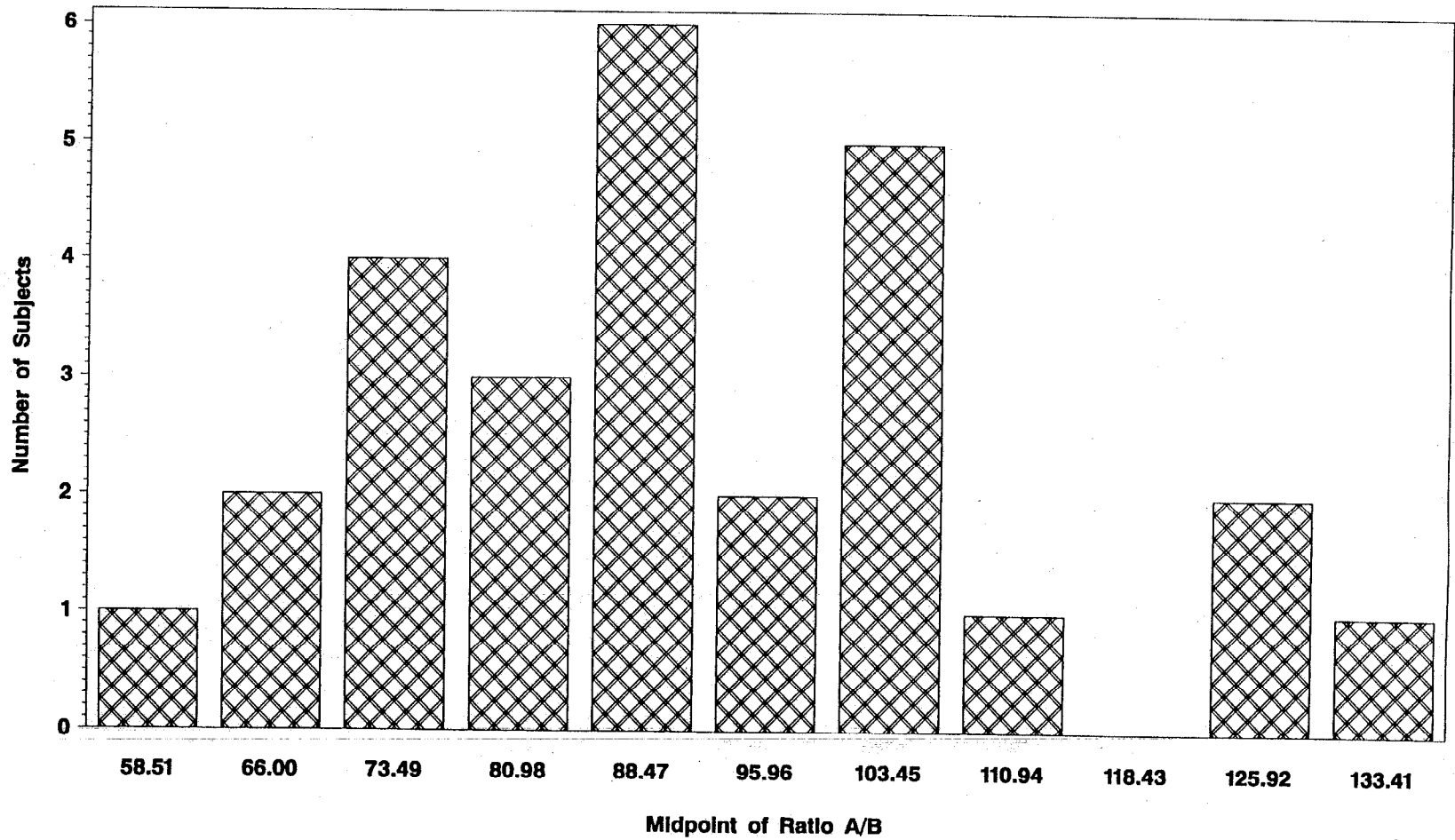


FIGURE 1.D

Distribution of Difference of Cmax Between Formulations for DILTIAZEM (STUDY # 2443)

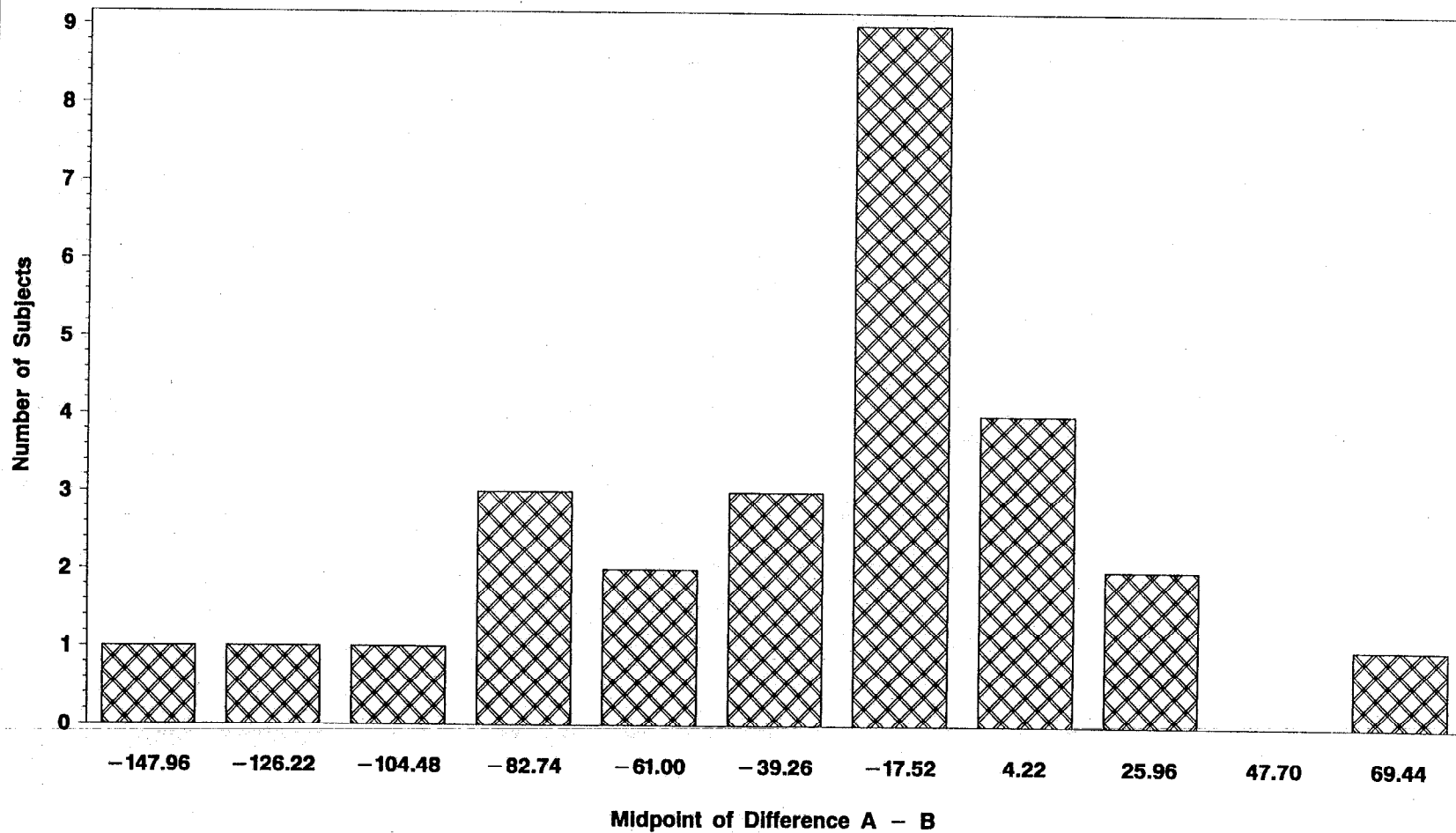


FIGURE 1.E

Distribution of Ratio of Cmax Between Formulations for DILTIAZEM (STUDY # 2443)

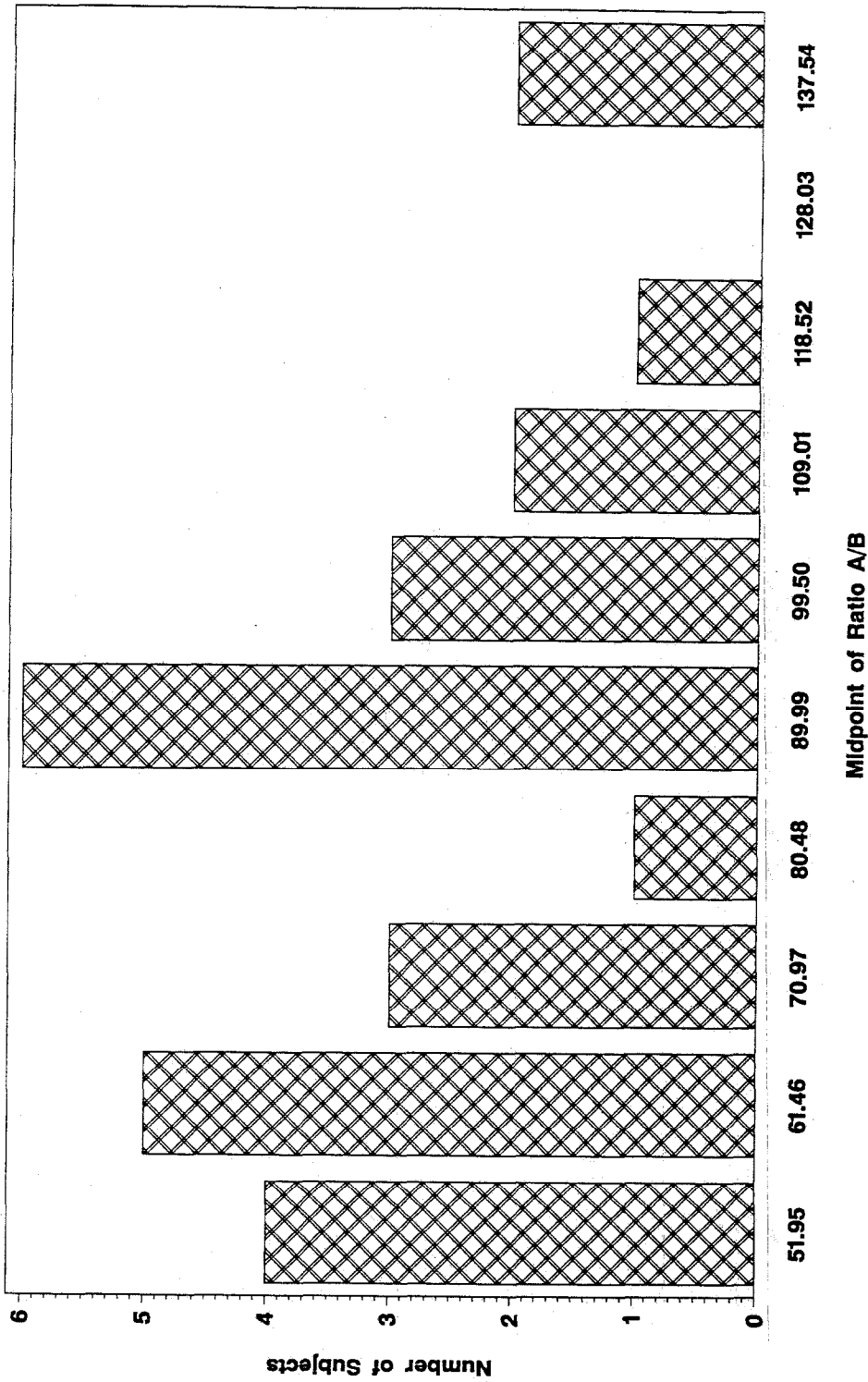


FIGURE 1.F

PLASMA DILTIAZEM CONCENTRATIONS

STUDY # 2443: ALL SUBJECTS IN TEST GROUP

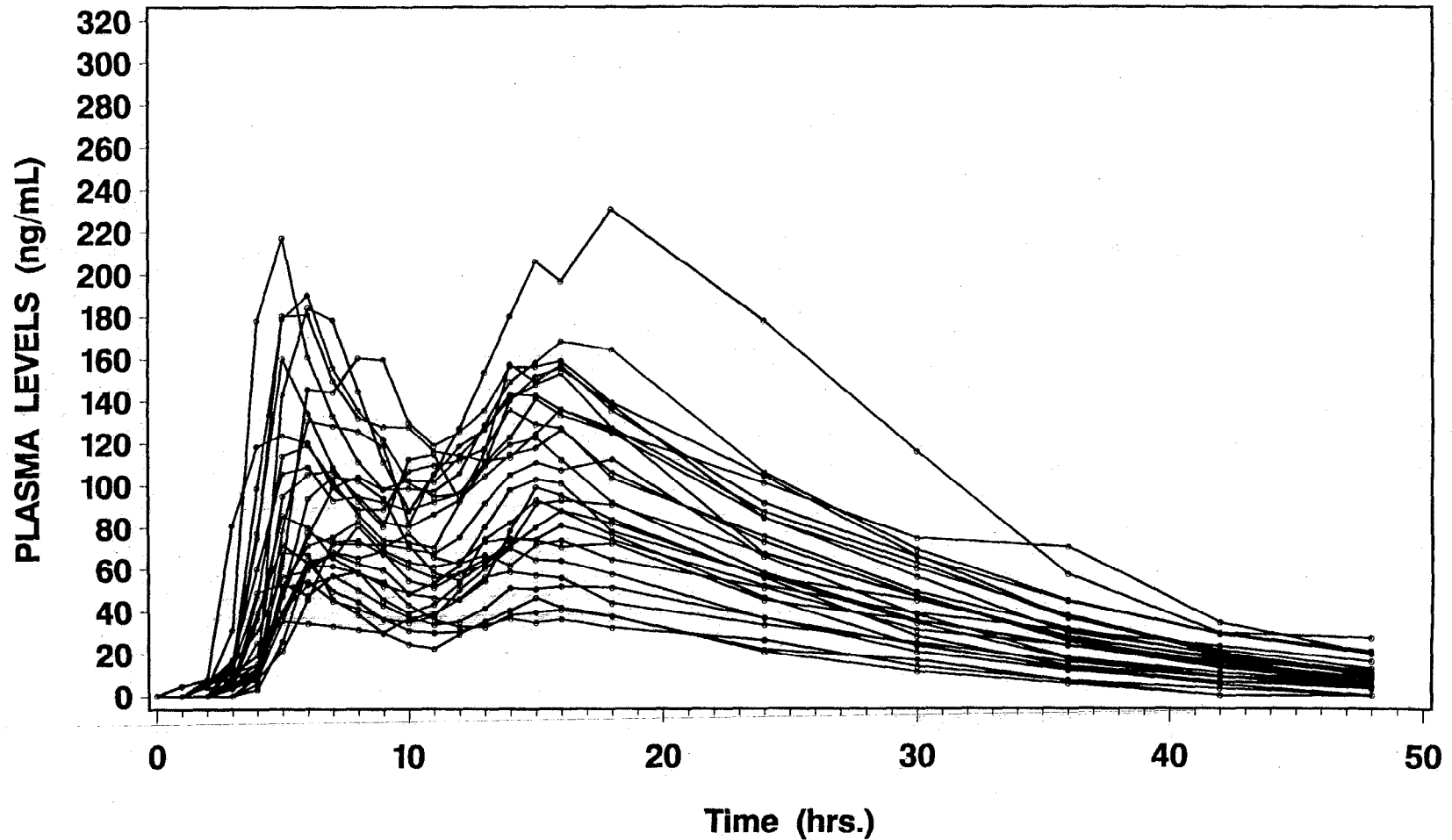


FIGURE 1.84

PLASMA DILTIAZEM CONCENTRATIONS
STUDY # 2443: ALL SUBJECTS IN REFERENCE GROUP

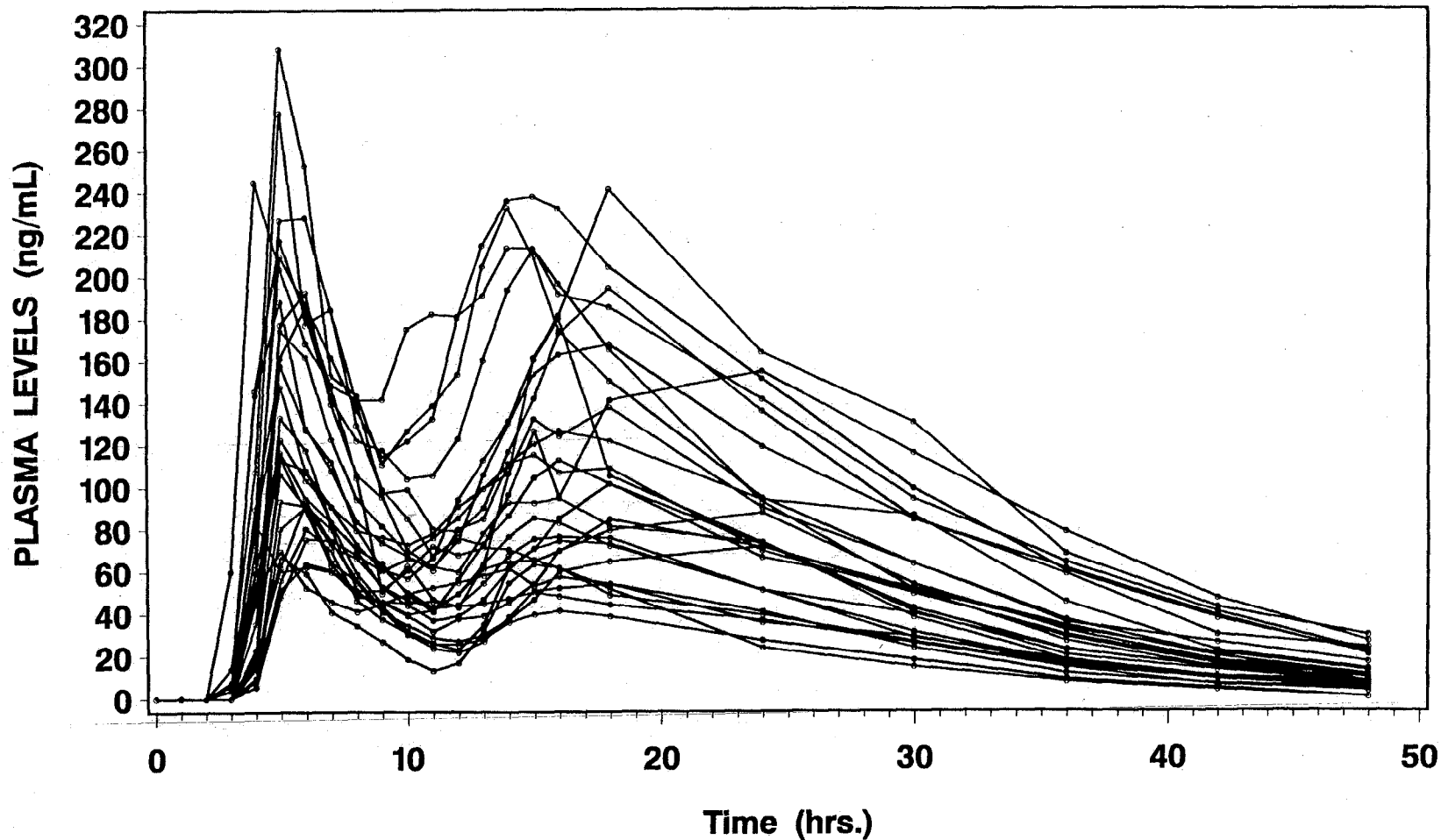


FIGURE 1.85

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS

STUDY # 2443: ALL SUBJECTS IN TEST GROUP

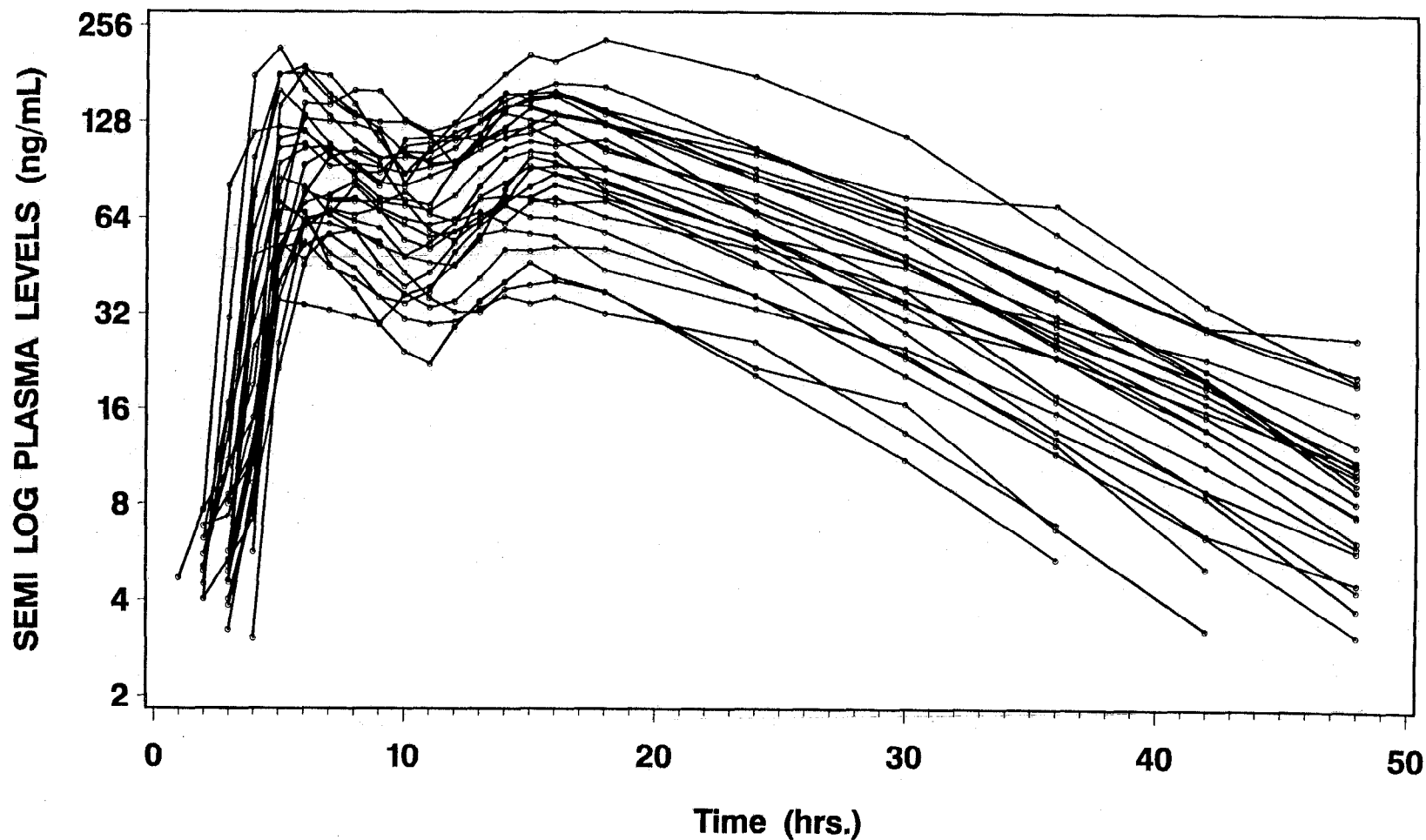


FIGURE 1.86

SEMI LOG PLASMA DILTIAZEM CONCENTRATIONS

STUDY # 2443: ALL SUBJECTS IN REFERENCE GROUP

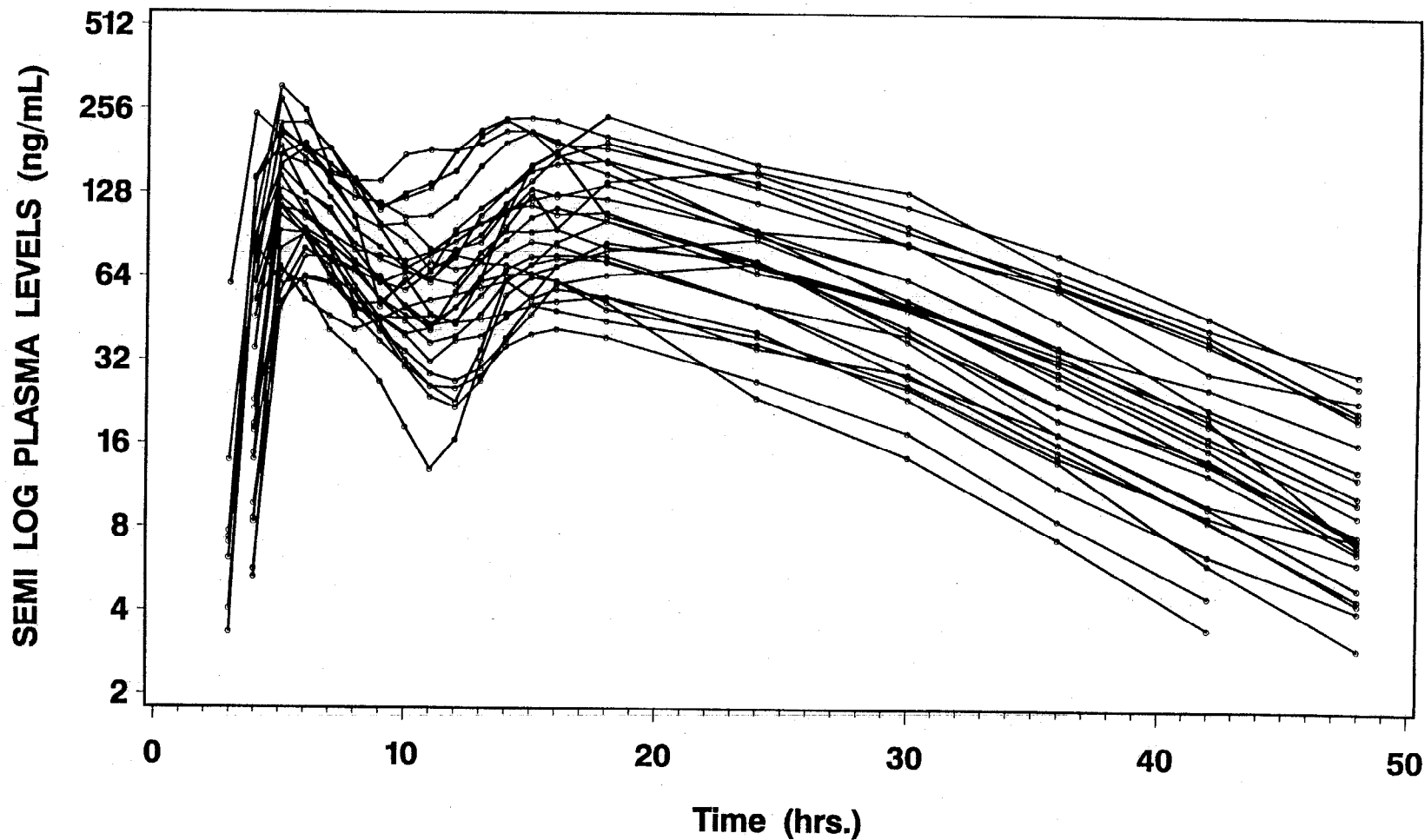


FIGURE 1.87

SECTION 2.0: PLASMA DESACETYLDILTIAZEM

TABLES

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
Study # 2443 (B01-527PK-DILG12)
TABLE 2. 1.

PLASMA DESACETYLDILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF ONE (1) CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg CAPSULE
(Andrx Pharmaceuticals, Inc. (A), Lot Number: 600A073, Expiry Date: 07/02)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION											
	0.00	1.00	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00	11.00
01	N.Q.	N.Q.	N.Q.	N.Q.	1.259	3.496	4.067	4.364	4.615	4.536	5.450	5.246
03	N.Q.	N.Q.	N.Q.**	N.Q.	N.Q.	1.395	3.703	5.139	5.514	6.732	4.812	6.592
04	N.Q.	N.Q.**	N.Q.	N.Q.	N.Q.	3.005	4.405	5.913	6.407	7.088	8.234	9.283
05	N.Q.	N.Q.	N.Q.	N.Q.	1.121	2.348	3.189	3.682	4.602	4.819	4.913	5.724
06	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.793	2.450	3.008	2.754	2.787
07	N.Q.	N.Q.	N.Q.	N.Q.	3.550	5.993	6.522	7.257	7.400	7.361	7.195	6.987
08	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.882	2.589	3.614	3.890	4.018	4.152
09	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.555	3.719	5.404	6.193	5.831	5.961
10	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.662	2.423	2.674	2.850	3.042	2.744	2.601
11	N.Q.	N.Q.	N.Q.	N.Q.	3.019	6.662	9.546	11.276	11.976	13.551	12.585	11.793
12	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.302	3.427	4.098	4.718	5.604	6.067	6.652
13	N.Q.	N.Q.	N.Q.	N.Q.	1.005	1.848	2.529	2.917	3.165	2.957	2.640	2.775
14	N.Q.	N.Q.	N.Q.	1.415	2.837	3.847	5.523	5.443	6.400	6.785	7.715	7.379
15	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.189	1.697	2.133	2.336	2.462	2.684	2.915
16	N.Q.	N.Q.	N.Q.	N.Q.	3.921	5.624	6.650	9.340	11.131	12.089	13.226	13.651**
17	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.964	4.367	5.212	5.337	6.866	5.767	5.656
18	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.741	3.296	3.846	4.953	5.020	5.501
19	N.Q.	N.Q.	N.Q.	N.Q.	1.954	4.996	7.147	8.048	8.490	8.516	8.806	8.510
20	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.480	3.227	3.502	4.754	5.159	5.507	5.375
21	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.705	3.193	3.665	3.723	3.393	2.902	3.492
22	N.Q.	N.Q.	N.Q.	N.Q.**	N.Q.	1.640	2.239	3.558	3.715	4.493	4.377	4.536
23	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.878	4.024	5.744	7.457	8.651	8.510	8.338
24	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.251	2.405	4.164	5.606	6.735	8.039	8.409
25	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.504	2.115	2.560	2.699	3.012	3.099
26	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.090	2.964	3.634	4.172	3.917	4.233
27	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.926	5.444	7.575	8.309	7.876	7.308	7.634
28	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.765	2.765	3.468	3.779	4.573	4.561
MEAN	0.000*	0.000*	0.000*	0.052*	0.691*	2.156*	3.602*	4.628	5.314	5.830	5.874	6.068
SD(±)	0.000*	0.000*	0.000*	0.272*	1.239*	1.942*	2.103*	2.345	2.497	2.727	2.799	2.741
C.V.(%)	0.000*	0.000*	0.000*	519.615*	179.201*	90.056*	58.370*	50.675	46.987	46.779	47.640	45.165
Range (Min.)	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	1.793	2.336	2.462	2.640	2.601
(Max.)	0.000	0.000	0.000	1.415	3.921	6.662	9.546	11.276	11.976	13.551	13.226	13.651
N =	27	27	27	27	27	27	27	27	27	27	27	27

Limit of quantitation = 0.999 ng/mL

N.Q. = Not quantifiable N.D. = No Data N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.Q.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 1. (Continued)

PLASMA DESACETYLDILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF ONE (1) CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg CAPSULE
 (Andrx Pharmaceuticals, Inc. (A), Lot Number: 600A073, Expiry Date: 07/02)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION										
	12.00	13.00	14.00	15.00	16.00	18.00	24.00	30.00	36.00	42.00	48.00
01	4.514	5.241	5.577	5.644	6.569	6.685	5.198	3.684	2.663	1.980	1.282
03	7.539	8.530	10.716**	12.178	12.124	16.523	16.237**	13.664	8.973	5.556	5.579
04	10.101**	11.063	13.883	14.592	15.816**	16.534	17.668	17.883	15.562**	12.645	11.238**
05	6.618	7.223	8.232	8.834	9.052	9.733	7.772	5.300	3.688	2.410	1.645
06	3.156	3.541	3.766	4.019	4.195	4.366	4.451	2.994	2.624	2.345	1.867
07	7.334	7.899	8.763	9.556	10.323	10.383	9.780	7.982	5.103	3.355	2.439
08	4.081	3.790	4.092	3.809	4.431	4.583	4.039	3.921	2.106	1.254	N.Q.
09	6.656	7.252	8.022	8.587	8.362	8.841	8.489	6.291	4.351	2.637	1.787
10	2.662	2.607	3.348	3.675	3.497	3.872	3.363	1.943	1.509	N.Q.	N.Q.
11	12.170	13.762	14.749	16.594	15.806	17.639	13.633	11.831	7.613	5.750	3.299
12	7.693	9.463	11.171	12.195	12.246	13.153	13.380	12.341	9.509	5.396	3.443
13	2.651	2.881	2.988	3.026	3.214	3.077	2.635	1.930	1.387	N.Q.	N.Q.
14	7.635	8.571	9.334	10.040	10.840	10.135	9.706	6.247	4.632	3.246	2.211
15	3.310	3.610	4.075	4.200	4.896	4.713	4.369	3.564	2.329	1.885	1.366
16	14.310	16.268	18.269	18.882	20.690	25.149	33.562	37.339	35.945	27.206	21.186
17	5.969	6.511	7.662	8.428	8.845	8.676	7.814	5.548	3.889	2.330	1.442
18	6.003	6.149	6.576	7.141	7.807	8.233	8.446	7.768	5.062	3.253	2.229**
19	8.878	9.366	9.235	9.441	10.462	10.897	11.277	8.964	9.291	5.442	3.750
20	5.975	7.160	8.400	8.758	8.522	9.357	9.162	6.305	3.526	2.199	1.482
21	3.797	4.756	5.421	6.684	6.616	7.359	7.216	4.387	2.788	1.675	1.506
22	5.026	6.021	6.451	6.691	6.431	7.751**	6.803	6.661	5.827	4.974	3.000
23	8.210	8.985	9.630	10.093	10.237	10.755	10.169	10.536	9.290	6.844	5.170
24	9.737	11.828	13.635	15.103	16.137	18.303	18.655	16.380	12.752	9.184	6.948
25	3.539	3.974	4.682	5.199	5.768	5.670	5.255	3.808	2.562	1.652	N.Q.
26	4.310	4.776	5.750	6.431	7.017	7.639	7.804	5.604	3.305	2.329	1.405
27	7.181	7.151	8.553	9.422	9.969	10.431	9.655	6.251	4.367	3.017	1.916
28	4.870	5.095**	4.991	5.304	5.841**	5.878	6.331	4.511	3.900	2.825	2.097
MEAN	6.442	7.166	8.073	8.686	9.100	9.864	9.736	8.283	6.465	4.496*	3.270*
SD(±)	2.891	3.339	3.819	4.132	4.294	5.184	6.342	7.149	6.863	5.302*	4.313*
C.V. (%)	44.876	46.599	47.310	47.574	47.181	52.555	65.140	86.305	106.158	117.930*	131.903*
Range (Min.)	2.651	2.607	2.988	3.026	3.214	3.077	2.635	1.930	1.387	0.000*	0.000*
(Max.)	14.310	16.268	18.269	18.882	20.690	25.149	33.562	37.339	35.945	27.206	21.186
N =	27	27	27	27	27	27	27	27	27	27	27

Limit of quantitation = 0.999 ng/mL

N.Q. = Not quantifiable N.D. = No Data N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.Q.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 2.

PLASMA DESACETYLDILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF 1 x 300 CARDIZEM® CD (DILTIAZEM HCl) CAPSULE
 (Aventis Pharmaceuticals, Inc. (B), Lot Number: 1030455, Expiry Date: 11/2002)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION											
	0.00	1.00	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00	11.00
01	N.Q.	N.Q.	N.Q.	N.Q.	1.760	5.579	6.847	5.926	6.949	5.968	5.658	6.204
03	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.985	5.370	6.751	6.540	3.637	5.841	4.727
04	N.Q.	N.Q.	N.Q.	N.Q.	1.972	10.453	9.832	13.975	12.555	11.772	11.764	10.101
05	N.Q.	N.Q.	N.Q.	N.Q.	1.396	3.614	4.380	5.259	5.058	5.510	5.249	4.778
06	N.Q.	N.Q.	N.D.	N.Q.	N.Q.	2.053	2.755	3.434	3.197	3.356	3.330	2.642
07	N.Q.	N.Q.	N.Q.	N.Q.	1.305	3.347	4.403	4.768	5.298	4.971	5.311	5.378
08	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.032	3.453	4.325	3.766	3.923	3.409	3.196
09	N.Q.	N.Q.	N.Q.	N.Q.	3.840	4.550	5.748	6.664	6.255	7.108	7.353	9.104
10	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.488	2.214	2.275	2.618	2.555	2.115	1.781
11	N.Q.	N.Q.	N.Q.	N.Q.	3.767	7.828	9.293	9.813	10.631	11.728	11.287	11.440
12	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.794	4.017	5.100	5.154	5.307	5.289	4.891
13	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.196	2.416	2.771	3.188	3.609	3.395	3.856
14	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.827	4.412	5.816	6.379	6.241	6.654	7.214
15	N.Q.	N.Q.	N.Q.	N.Q.	2.339	1.821	2.871	3.631	3.729	3.737	3.737	4.693
16	N.Q.	N.Q.	N.Q.	N.Q.	2.507	5.334	6.194	7.509	7.836	9.517	10.862	12.011
17	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.817	2.874	3.178	3.665	3.465	3.568	3.519
18	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.581	3.484	3.932	4.486	4.094	3.817	3.483
19	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	4.254	7.249	7.292	7.566	8.107	6.582	6.090
20	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.526	3.017	4.222	4.586	4.799	5.505	5.824
21	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	1.350	2.747	3.415	3.739	3.479	3.162	2.967
22	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.423	3.337	3.814	4.403	4.873	4.263	3.654
23	N.Q.	N.Q.	N.Q.	N.Q.	4.323	8.106**	7.974	9.971	8.428	8.134	7.560	6.982
24	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	5.369	8.152	9.797	8.855	8.218	9.266	8.805
25	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.392	3.573	3.365	3.118	3.255	3.163	3.197
26	N.Q.	N.Q.	N.Q.	N.Q.	1.466	3.522	4.842	5.382	5.465	5.270	4.910	5.599
27	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	3.767	7.107	6.441	6.434	6.763	6.060	6.201
28	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	2.217	3.611	4.125	4.425	4.246	4.215	3.659
MEAN	0.000*	0.000*	0.000*	0.000*	0.914*	3.564	4.895	5.665	5.716	5.690	5.679	5.629
SD (±)	0.000*	0.000*	0.000*	0.000*	1.381*	2.299	2.204	2.706	2.415	2.506	2.592	2.686
C.V. (%)	0.000*	0.000*	0.000*	0.000*	151.360*	64.509	45.029	47.766	42.249	44.046	45.644	47.711
Range (Min.)	0.000*	0.000*	0.000*	0.000*	0.000*	1.196	2.214	2.275	2.618	2.555	2.115	1.781
(Max.)	0.000	0.000	0.000	0.000	4.323	10.453	9.832	13.975	12.555	11.772	11.764	12.011
N =	27	27	26	27	27	27	27	27	27	27	27	27

Limit of quantitation = 0.999 ng/mL

N.Q. = Not quantifiable N.D. = No Data N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.Q.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527FK-DILG12)
 TABLE 2. 2. (Continued)

PLASMA DESACETYLDILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF 1 x 300 CARDIZEM® CD (DILTIAZEM HCl) CAPSULE
 (Aventis Pharmaceuticals, Inc. (B), Lot Number: 1030455, Expiry Date: 11/2002)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION										
	12.00	13.00	14.00	15.00	16.00	18.00	24.00	30.00	36.00	42.00	48.00
01	6.898	8.154	9.123	9.628	9.092	9.565	8.022	4.665	3.641	2.338	1.307**
03	4.376	4.717	6.032	7.422	8.046	12.780	15.907	12.835	9.461	7.818	5.968
04	10.714	8.490**	10.011	12.387**	10.120**	14.169	22.926	25.750	25.496	20.358**	15.653**
05	5.244	5.814	6.739	7.101	7.109	8.403	7.147	6.604	4.426	2.380	1.505
06	2.899	2.968	3.015	2.851	3.304	4.550	4.870	4.229	3.114	2.276	1.759
07	5.439	6.031	6.818	7.119	6.878	8.207	7.717	5.904	4.367	2.647	1.799
08	2.962	3.342	3.605	4.286	4.568	5.541	5.721	5.744	4.152	2.891	1.701
09	8.996	9.681	11.721	12.633	11.607	11.165	9.676	5.357	3.583	2.361	1.524
10	1.951	1.978	2.463	3.052	3.688	4.095	3.893	2.401	1.623	1.043	N.Q.
11	12.599	14.128	16.990	19.458	19.559	21.392	22.241	19.621	15.359	10.835	6.822
12	4.918	5.165	5.773	6.194	6.260	6.626	7.060	6.339	4.430	3.049	2.053
13	3.794	4.084	3.899	4.126	3.570	4.172	3.884	3.262	2.382	1.344	N.Q.
14	7.360	8.486	9.152	10.693	11.211	10.730	12.264	8.616	6.156	4.529	2.914
15	4.298	5.353	5.709	5.932	6.164	5.462	5.875	4.059**	2.575	1.999	1.399
16	13.883	16.429	18.598	17.384	21.058	22.927	30.931	34.656	27.103	22.442	19.821
17	3.388	3.663	4.255	4.999	5.001	6.028	6.344	5.491**	3.567	2.604	1.404
18	3.490	3.485	3.597	3.808	4.202	5.237	7.605	7.031	5.330	3.465	2.242
19	6.511	6.897	8.875	10.213	10.315	12.340	13.033	11.442	9.100	6.490	3.993
20	5.671	6.164	7.491	7.840	8.292	7.945	9.855	6.897	3.988	2.907	1.966
21	2.577	2.999	3.311	4.266	4.815	5.702	6.786	4.778	3.060	2.211	1.814
22	4.290	5.395	5.905	7.184	8.113	8.538	9.429	8.111	6.314	4.458	3.105
23	7.405	7.211	7.673	7.745	7.854	10.231	12.078	11.413	9.302	7.109	4.974
24	8.798	9.050	10.341	11.514	13.138	16.186	18.289	17.417	14.941	9.482	7.976
25	3.465	3.597	4.356	4.808	4.761	5.376	4.874	3.661	2.397	1.606	1.079
26	6.824	7.322	8.744	10.004	11.532	9.330	10.273	6.761	3.893	2.492	1.601
27	6.751**	6.459	6.754	8.388	8.571**	9.408	8.506	6.817	4.358	3.249	2.531
28	4.347	4.229	3.989	4.325	5.060	6.060	7.190	5.417	3.581	2.748	1.609
MEAN	5.920	6.344	7.220	7.979	8.292	9.339	10.459	9.084	6.952	5.079	3.649*
SD(±)	3.009	3.309	3.941	4.139	4.423	4.857	6.505	7.411	6.566	5.319	4.522*
C.V.(%)	50.825	52.163	54.582	51.874	53.343	52.001	62.195	81.579	94.449	104.724	123.918*
Range (Min.)	1.951	1.978	2.463	2.851	3.304	4.095	3.884	2.401	1.623	1.043	0.000*
(Max.)	13.883	16.429	18.598	19.458	21.058	22.927	30.931	34.656	27.103	22.442	19.821
N =	27	27	27	27	27	27	27	27	27	27	27

Limit of quantitation = 0.999 ng/mL

N.Q. = Not quantifiable N.D. = No Data N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.Q.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 3.

SUMMARY OF DESACETYLDILTIAZEM PARAMETERS FOR EACH SUBJECT GIVEN THE ONE (1) CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg CAPSULE
 (Andrx Pharmaceuticals, Inc. (A), Lot Number: 600A073, Expiry Date: 07/02)

SUBJECT	SEQ	PERIOD	C _{max} (ng/mL)	T _{max} (hrs)	AUC(0-t) (ng.hr/mL)	AUC(0-inf) (ng.hr/mL)	AUC(0-t)		K _{a1} (hr ⁻¹)	T _{half} (hrs)
							-----(%)	AUC(0-inf)		
01	AB	1	6.69	18.00	175.60	198.09	88.65	0.057	12.16	
03	AB	1	16.52	18.00	440.44	N.C.	N.C.	N.C.	N.C.	
04	BA	2	17.88	30.00	600.29	1014.66	59.16	0.027	25.56	
05	BA	2	9.73	18.00	233.77	259.12	90.22	0.065	10.68	
06	BA	2	4.45	24.00	131.12	204.37	64.16	0.025	27.20	
07	BA	2	10.38	18.00	307.47	344.27	89.31	0.066	10.46	
08	AB	1	4.58	18.00	125.05	143.27	87.29	0.069	10.07	
09	BA	2	8.84	18.00	244.06	269.13	90.68	0.071	9.72	
10	AB	1	3.87	18.00	87.38	109.98	79.45	0.067	10.38	
11	AB	1	17.64	18.00	474.81	523.94	90.79	0.069	10.11	
12	AB	1	13.38	24.00	398.46	445.45	89.45	0.073	9.46	
13	BA	2	3.21	16.00	80.06	110.86	72.22	0.045	15.39	
14	AB	1	10.84	16.00	289.34	326.06	88.74	0.060	11.51	
15	AB	1	4.90	16.00	133.79	161.46	82.86	0.049	14.04	
16	BA	2	37.34	30.00	1142.85	1623.76	70.38	0.044	15.73	
17	AB	1	8.85	16.00	234.52	253.52	92.51	0.076	9.13	
18	AB	1	8.45	24.00	248.78	280.74	88.61	0.070	9.94	
19	BA	2	11.28	24.00	373.76	423.36	88.28	0.076	9.17	
20	AB	1	9.36	18.00	241.11	260.04	92.72	0.078	8.85	
21	AB	1	7.36	18.00	183.01	205.06	89.24	0.068	10.15	
22	AB	1	7.75	18.02	243.98	298.21	81.82	0.055	12.53	
23	BA	2	10.76	18.00	376.44	503.50	74.76	0.041	17.04	
24	BA	2	18.66	24.00	547.00	690.70	79.20	0.048	14.34	
25	BA	2	5.77	16.00	138.42	164.05	84.38	0.064	10.75	
26	BA	2	7.80	24.00	201.83	220.56	91.51	0.075	9.24	
27	BA	2	10.43	18.00	281.54	310.55	90.66	0.066	10.49	
28	BA	2	6.33	24.00	185.13	233.15	79.41	0.044	15.87	
MEAN			10.48	20.07	300.74	368.34	83.71	0.06	12.69	
SD(±)			6.87	4.13	215.98	322.78	9.05	0.01	4.69	
C.V.(%)			65.57	20.58	71.82	87.63	10.81	24.90	36.93	
Range(Min.)			3.21	16.00	80.06	109.98	59.16	0.03	8.85	
(Max.)			37.34	30.00	1142.85	1623.76	92.72	0.08	27.20	
Num of subjects			27	27	27	26	26	26	26	

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 4.

SUMMARY OF DESACETYLDILTIAZEM PARAMETERS FOR EACH SUBJECT GIVEN THE CARDIZEM® CD (DILTIAZEM HCl) CAPSULE
 (Aventis Pharmaceuticals, Inc. (B), Lot Number: 1030455, Expiry Date: 11/2002)

SUBJECT	SEQ	PERIOD	C _{max} (ng/mL)	T _{max} (hrs)	AUC(0-t) (ng.hr/mL)	AUC(0-inf) (ng.hr/mL)	AUC(0-t)	K _{e1} (hr ⁻¹)	T _{1/2t} (hrs)
							-----(% AUC(0-inf)		
01	AB	2	9.63	15.00	246.54	264.70	93.14	0.072	9.63
03	AB	2	15.91	24.00	415.62	559.54	74.28	0.041	16.72
04	BA	1	25.75	30.00	810.35	1195.92	67.76	0.041	17.07
05	BA	1	8.40	18.00	232.35	250.21	92.86	0.084	8.22
06	BA	1	4.87	24.00	147.87	183.70	80.49	0.049	14.12
07	BA	1	8.21	18.00	232.54	259.09	89.75	0.068	10.23
08	AB	2	5.74	30.00	183.47	206.34	88.91	0.074	9.32
09	BA	1	12.63	15.00	286.16	307.99	92.91	0.070	9.93
10	AB	2	4.10	18.00	97.03	111.44	87.07	0.072	9.58
11	AB	2	22.24	24.00	682.67	799.01	85.44	0.059	11.82
12	AB	2	7.06	24.00	220.92	253.72	87.07	0.063	11.07
13	BA	1	4.17	18.00	119.58	142.63	83.84	0.058	11.89
14	AB	2	12.26	24.00	333.10	382.23	87.15	0.059	11.68
15	AB	2	6.16	16.00	170.22	193.67	87.89	0.060	11.62
16	BA	1	34.66	30.00	1001.61	1761.76	56.85	0.026	26.58
17	AB	2	6.34	24.00	182.28	201.38	90.51	0.073	9.43
18	AB	2	7.61	24.00	214.82	249.67	86.04	0.064	10.78
19	BA	1	13.03	24.00	396.84	465.36	85.27	0.058	11.90
20	AB	2	9.86	24.00	248.64	277.54	89.59	0.068	10.19
21	AB	2	6.79	24.00	170.49	204.19	83.50	0.054	12.87
22	AB	2	9.43	24.00	275.05	332.75	82.66	0.054	12.88
23	BA	1	12.08	24.00	398.52	506.63	78.66	0.046	15.07
24	BA	1	18.29	24.00	567.32	738.37	76.83	0.047	14.87
25	BA	1	5.38	18.00	145.40	161.32	90.13	0.068	10.23
26	BA	1	11.53	16.00	269.29	289.65	92.97	0.079	8.82
27	BA	1	9.41	18.00	266.77	314.74	84.76	0.053	13.14
28	BA	1	7.19	24.00	193.66	218.37	88.68	0.065	10.65
MEAN			11.06	22.07	315.15	401.18	84.63	0.06	12.23
SD(±)			7.09	4.45	216.80	361.57	8.19	0.01	3.68
C.V.(%)			64.13	20.14	68.79	90.13	9.68	21.75	30.08
Range(Min.)			4.10	15.00	97.03	111.44	56.85	0.03	8.22
(Max.)			34.66	30.00	1001.61	1761.76	93.14	0.08	26.58
Num of subjects			27	27	27	27	27	27	27

N.C. - No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 5.

AREA UNDER THE PLASMA DESACETYLDILTIAZEM CONCENTRATION-TIME CURVES (0-t hrs.)

SUBJECT No.	RAW SCALE			RATIO% #	LOG SCALE		
	CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg	DIFF		CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg	DIFF *
01	175.60	246.54	-70.94	71.23	5.1682	5.5075	-0.3393
03	440.44	415.62	24.82	105.97	6.0878	6.0298	0.0580
04	600.29	810.35	-210.06	74.08	6.3974	6.6975	-0.3000
05	233.77	232.35	1.42	100.61	5.4543	5.4483	0.0061
06	131.12	147.87	-16.75	88.67	4.8761	4.9963	-0.1202
07	307.47	232.54	74.93	132.22	5.7284	5.4491	0.2793
08	125.05	183.47	-58.41	68.16	4.8287	5.2120	-0.3833
09	244.06	286.16	-42.10	85.29	5.4974	5.6565	-0.1591
10	87.38	97.03	-9.65	90.06	4.4703	4.5751	-0.1047
11	474.81	682.67	-207.86	69.55	6.1629	6.5260	-0.3631
12	398.46	220.92	177.53	180.36	5.9876	5.3978	0.5898
13	80.06	119.58	-39.52	66.95	4.3828	4.7840	-0.4012
14	289.34	333.10	-43.76	86.86	5.6676	5.8085	-0.1408
15	133.79	170.22	-36.43	78.60	4.8962	5.1371	-0.2408
16	1142.85	1001.61	141.24	114.10	7.0413	6.9094	0.1319
17	234.52	182.28	52.25	128.66	5.4576	5.2055	0.2520
18	248.78	214.82	33.96	115.81	5.5165	5.3698	0.1467
19	373.76	396.84	-23.08	94.19	5.9236	5.9835	-0.0599
20	241.11	248.64	-7.54	96.97	5.4852	5.5160	-0.0308
21	183.01	170.49	12.51	107.34	5.2095	5.1387	0.0708
22	243.98	275.05	-31.07	88.71	5.4971	5.6170	-0.1198
23	376.44	398.52	-22.08	94.46	5.9308	5.9878	-0.0570
24	547.00	567.32	-20.32	96.42	6.3044	6.3409	-0.0365
25	138.42	145.40	-6.98	95.20	4.9303	4.9795	-0.0492
26	201.83	269.29	-67.46	74.95	5.3074	5.5958	-0.2884
27	281.54	266.77	14.78	105.54	5.6403	5.5864	0.0539
28	185.13	193.66	-8.53	95.60	5.2211	5.2661	-0.0450
MEAN	300.74	315.15	-14.41	96.54	5.5211	5.5823	-0.0611
SD(±)	215.98	216.80	79.95	24.06	0.6030	0.5654	0.2256
C.V.(%)	71.82	68.79	554.80	24.93	10.9221	10.1287	369.0021
Range (Min.)	80.06	97.03	-210.06	66.95	4.3828	4.5751	-0.4012
(Max.)	1142.85	1001.61	177.53	180.36	7.0413	6.9094	0.5898
Num of subjects	27	27	27	27	27	27	27
Geometric Mean					249.9098	265.6820	

RATIO% = (CARTIA XTTM / CARDIZEM[®] CD) × 100

* DIFF(Log Scale) = ln(CARTIA XTTM) - ln(CARDIZEM[®] CD)

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 6.

ANOVA ON DESACETYLDILTIAZEM LOG AUC (0 - t hrs.)

The GLM Procedure

Dependent Variable: lauct

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	17.15822377	0.61279371	23.25	<.0001
Error	25	0.65895763	0.02635831		
Corrected Total	53	17.81718140			

R-Square	Coeff Var	Root MSE	lauct Mean
0.963016	2.924365	0.162352	5.551714

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.61034285	0.61034285	23.16	<.0001
subj (sq)	25	16.49476007	0.65979040	25.03	<.0001
peri	1	0.00266160	0.00266160	0.10	0.7533
drug	1	0.04953585	0.04953585	1.88	0.1826

The GLM Procedure
 Least Squares Means

drug	lauct LSMEAN	Standard Error	Pr > t
A	5.51746557	0.03126619	<.0001
B	5.57808209	0.03126619	<.0001

sq	lauct LSMEAN	Standard Error	Pr > t
AB	5.44138694	0.03183993	<.0001
BA	5.65416072	0.03068172	<.0001

peri	lauct LSMEAN	Standard Error	Pr > t
1	5.55479925	0.03126619	<.0001
2	5.54074841	0.03126619	<.0001

The GLM Procedure

Dependent Variable: lauct

Tests of Hypotheses Using the Type III MS for subj (sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.61034285	0.61034285	0.93	0.3454

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	-0.06061652	0.04421707	-1.37	0.1826

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 7.

90% GEOMETRIC CONFIDENCE INTERVAL BASED ON AREA UNDER THE PLASMA DESACETYLDILTIAZEM
 CONCENTRATION-TIME CURVES

LOG AUC (0-t) (ng.hr/mL)

Source	DF	TYPE III SS	Mean Square	F Value	Pr > F
ERROR	25	0.658958	0.026358	.	.
sq	1	0.610343	0.610343	23.155618	0.000061
subj(sq)	25	16.494760	0.659790	25.031594	0.000000
peri	1	0.002662	0.002662	0.100977	0.753299
drug	1	0.049536	0.049536	1.879326	0.182594

INTRA-SUBJECT C.V. = $100 \times \text{SQRT}(\text{MSE}) = 100 \times \text{SQRT}(0.026358) = 16.24 \%$

DIFFERENCE = TEST - REFERENCE = $5.517466 - 5.578082 = -.060617$

SE DIFFERENCE = 0.044217

AUC(0-t) RATIO = $100 \times e^{\frac{(\text{difference})}{\text{SE DIFFERENCE}}} = 100 \times e^{\frac{(5.517466 - 5.578082)}{0.044217}} = 94.12 \%$

90% GEOMETRIC CONFIDENCE INTERVAL

LOWER, UPPER = $100 \times e^{(\text{difference} \pm t_{0.05, 25} \times \text{SE difference})}$

LOWER = $100 \times e^{(-.060617 - 1.7081 \times 0.044217)} = 87.27 \%$

UPPER = $100 \times e^{(-.060617 + 1.7081 \times 0.044217)} = 101.50 \%$

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 8.

AREA UNDER THE PLASMA DESACETYLDILTIAZEM CONCENTRATION-TIME CURVES (0 - infinity)

AUC (0-inf) (ng.hr/mL)

SUBJECT No.	RAW SCALE			RATIO% #	LOG SCALE		
	CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg	DIFF		CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg	DIFF *
01	198.09	264.70	-66.62	74.83	5.2887	5.5786	-0.2899
03	N.C.	559.54	N.C.	N.C.	N.C.	6.3271	N.C.
04	1014.66	1195.92	-181.25	84.84	6.9223	7.0867	-0.1644
05	259.12	250.21	8.91	103.56	5.5573	5.5223	0.0350
06	204.37	183.70	20.67	111.25	5.3199	5.2133	0.1066
07	344.27	259.09	85.19	132.88	5.8414	5.5572	0.2843
08	143.27	206.34	-63.07	69.43	4.9647	5.3295	-0.3648
09	269.13	307.99	-38.86	87.38	5.5952	5.7301	-0.1349
10	109.98	111.44	-1.46	98.69	4.7003	4.7135	-0.0132
11	522.94	799.01	-276.07	65.45	6.2595	6.6834	-0.4239
12	445.45	253.72	191.73	175.57	6.0991	5.5362	0.5628
13	110.86	142.63	-31.77	77.73	4.7083	4.9603	-0.2520
14	326.06	382.23	-56.17	85.30	5.7871	5.9460	-0.1589
15	161.46	193.67	-32.21	83.37	5.0842	5.2662	-0.1819
16	1623.76	1761.76	-138.00	92.17	7.3925	7.4741	-0.0816
17	253.52	201.38	52.14	125.89	5.5354	5.3052	0.2303
18	280.74	249.67	31.07	112.44	5.6374	5.5202	0.1173
19	423.36	465.36	-42.00	90.97	6.0482	6.1428	-0.0946
20	260.04	277.54	-17.51	93.69	5.5608	5.6260	-0.0652
21	205.06	204.19	0.88	100.43	5.3233	5.3190	0.0043
22	298.21	332.75	-34.54	89.62	5.6978	5.8074	-0.1096
23	503.50	506.63	-3.13	99.38	6.2216	6.2278	-0.0062
24	690.70	738.37	-47.67	93.54	6.5377	6.6044	-0.0667
25	164.05	161.32	2.72	101.69	5.1002	5.0834	0.0167
26	220.56	289.65	-69.10	76.15	5.3962	5.6687	-0.2725
27	310.55	314.74	-4.19	98.67	5.7384	5.7518	-0.0134
28	233.15	218.37	14.77	106.76	5.4517	5.3862	0.0655
MEAN	368.34	401.18	-26.75	97.37	5.6834	5.7543	-0.0489
SD(±)	322.78	361.57	85.65	22.51	0.6293	0.6419	0.2092
C.V. (%)	87.63	90.13	320.16	23.12	11.0732	11.1555	427.9934
Range (Min.)	109.98	111.44	-276.07	65.45	4.7003	4.7135	-0.4239
(Max.)	1623.76	1761.76	191.73	175.57	7.3925	7.4741	0.5628
Num of subjects	26	27	26	26	26	27	26
Geometric Mean					293.9472	315.5446	

RATIO% = (CARTIA XTTM / CARDIZEM[®] CD) × 100

* DIFF(Log Scale) = ln(CARTIA XTTM) - ln(CARDIZEM[®] CD)

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 9.

ANOVA ON DESACETYLDILTIAZEM LOG AUC (0 - inf)

The GLM Procedure

NOTE: Due to missing values, only 53 observations can be used in this analysis.

The GLM Procedure

Dependent Variable: lauci

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	20.13568317	0.71913154	31.60	<.0001
Error	24	0.54625445	0.02276060		
Corrected Total	52	20.68193762			

R-Square	Coeff Var	Root MSE	lauci Mean
0.973588	2.637726	0.150866	5.719555

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	1.03058150	1.03058150	45.28	<.0001
subj(sq)	25	18.76994951	0.75079798	32.99	<.0001
peri	1	0.00087253	0.00087253	0.04	0.8464
drug	1	0.03168320	0.03168320	1.39	0.2496

The GLM Procedure
Least Squares Means

drug	lauci LSMEAN	Standard Error	Pr > t
A	5.69975008	0.03028356	<.0001
B	5.74926449	0.02905414	<.0001

sq	lauci LSMEAN	Standard Error	Pr > t
AB	5.58330939	0.03079543	<.0001
BA	5.86570517	0.02851103	<.0001

peri	lauci LSMEAN	Standard Error	Pr > t
1	5.72039883	0.03028356	<.0001
2	5.72861573	0.02905414	<.0001

The GLM Procedure

Dependent Variable: lauci

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	1.03058150	1.03058150	1.37	0.2524

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	-0.04951440	0.04196710	-1.18	0.2496

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 10.

90% GEOMETRIC CONFIDENCE INTERVAL BASED ON AREA UNDER THE PLASMA DESACETYLDILTIAZEM
 CONCENTRATION-TIME CURVES

LOG AUC (0-inf) (ng.hr/mL)

Source	DF	TYPE III SS	Mean Square	F Value	Pr > F
ERROR	24	0.546254	0.022761	.	.
sq	1	1.030582	1.030582	45.279185	0.000001
subj (sq)	25	18.769950	0.750798	32.986736	0.000000
peri	1	0.000873	0.000873	0.038335	0.846420
drug	1	0.031683	0.031683	1.392019	0.249627

INTRA-SUBJECT C.V. = $100 \times \text{SQRT}(\text{MSE}) = 100 \times \text{SQRT}(0.022761) = 15.09 \%$

DIFFERENCE = TEST - REFERENCE = $5.699750 - 5.749264 = -.049514$

SE DIFFERENCE = 0.041967

AUCINF RATIO = $100 \times e^{\frac{(\text{difference})}{\text{SE difference}}}$ = $100 \times e^{\frac{(5.699750 - 5.749264)}{0.041967}}$ = 95.17 %

90% GEOMETRIC CONFIDENCE INTERVAL

LOWER, UPPER = $100 \times e^{(\text{difference} \pm t_{0.05, 24} \times \text{SE difference})}$

LOWER = $100 \times e^{(-.049514 - 1.7109 \times 0.041967)}$ = 88.58 %

UPPER = $100 \times e^{(-.049514 + 1.7109 \times 0.041967)}$ = 102.25 %

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 11.

PEAK PLASMA DESACETYLDILTIAZEM CONCENTRATIONS

SUBJECT No.	RAW SCALE			RATIO% #	LOG SCALE		
	CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg	DIFF		CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg	DIFF *
01	6.69	9.63	-2.94	69.43	1.8999	2.2647	-0.3648
03	16.52	15.91	0.62	103.87	2.8048	2.7668	0.0380
04	17.88	25.75	-7.87	69.45	2.8839	3.2484	-0.3646
05	9.73	8.40	1.33	115.83	2.2755	2.1286	0.1469
06	4.45	4.87	-0.42	91.40	1.4931	1.5831	-0.0900
07	10.38	8.21	2.18	126.51	2.3402	2.1050	0.2352
08	4.58	5.74	-1.16	79.79	1.5224	1.7482	-0.2258
09	8.84	12.63	-3.79	69.98	2.1794	2.5363	-0.3569
10	3.87	4.10	-0.22	94.55	1.3538	1.4098	-0.0560
11	17.64	22.24	-4.60	79.31	2.8701	3.1019	-0.2318
12	13.38	7.06	6.32	189.52	2.5938	1.9544	0.6393
13	3.21	4.17	-0.96	77.04	1.1675	1.4284	-0.2609
14	10.84	12.26	-1.42	88.39	2.3832	2.5067	-0.1234
15	4.90	6.16	-1.27	79.43	1.5884	1.8187	-0.2303
16	37.34	34.66	2.68	107.74	3.6200	3.5455	0.0746
17	8.85	6.34	2.50	139.42	2.1799	1.8475	0.3323
18	8.45	7.61	0.84	111.06	2.1337	2.0288	0.1049
19	11.28	13.03	-1.76	86.53	2.4228	2.5675	-0.1447
20	9.36	9.86	-0.50	94.95	2.2361	2.2880	-0.0519
21	7.36	6.79	0.57	108.44	1.9959	1.9149	0.0811
22	7.75	9.43	-1.68	82.20	2.0478	2.2438	-0.1960
23	10.76	12.08	-1.32	89.05	2.3754	2.4914	-0.1160
24	18.66	18.29	0.37	102.00	2.9261	2.9063	0.0198
25	5.77	5.38	0.39	107.29	1.7523	1.6819	0.0704
26	7.80	11.53	-3.73	67.67	2.0546	2.4451	-0.3905
27	10.43	9.41	1.02	110.87	2.3448	2.2416	0.1032
28	6.33	7.19	-0.86	88.05	1.8455	1.9727	-0.1272
MEAN	10.48	11.06	-0.58	97.40	2.1960	2.2510	-0.0550
SD(±)	6.87	7.09	2.69	25.88	0.5465	0.5391	0.2357
C.V.(%)	65.57	64.13	463.48	26.57	24.8859	23.9477	428.5819
Range (Min.)	3.21	4.10	-7.87	67.67	1.1675	1.4098	-0.3905
(Max.)	37.34	34.66	6.32	189.52	3.6200	3.5455	0.6393
Num of subjects	27	27	27	27	27	27	27
Geometric Mean					8.9890	9.4972	

RATIO% = (CARTIA XT™ / CARDIZEM® CD) × 100

* DIFF (Log Scale) = ln(CARTIA XT™) - ln(CARDIZEM® CD)

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 12

ANOVA ON DESACETYLDILTIAZEM LOG C_{max}

The GLM Procedure

Dependent Variable: lc_{max}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	14.65193725	0.52328347	18.46	<.0001
Error	25	0.70865380	0.02834615		
Corrected Total	53	15.36059105			

R-Square	Coeff Var	Root MSE	lc _{max} Mean
0.953865	7.572138	0.168363	2.223456

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.39446850	0.39446850	13.92	0.0010
subj(sq)	25	14.20286984	0.56811479	20.04	<.0001
peri	1	0.01375691	0.01375691	0.49	0.4925
drug	1	0.03905023	0.03905023	1.38	0.2516

The GLM Procedure
 Least Squares Means

drug	lc _{max} LSMEAN	Standard Error	Pr > t
A	2.19337845	0.03242375	<.0001
B	2.24719836	0.03242375	<.0001

sq	lc _{max} LSMEAN	Standard Error	Pr > t
AB	2.13476059	0.03301873	<.0001
BA	2.30581621	0.03181765	<.0001

peri	lc _{max} LSMEAN	Standard Error	Pr > t
1	2.23626049	0.03242375	<.0001
2	2.20431631	0.03242375	<.0001

The GLM Procedure

Dependent Variable: lc_{max}

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.39446850	0.39446850	0.69	0.4126

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	-0.05381991	0.04585411	-1.17	0.2516

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 13.

90% GEOMETRIC CONFIDENCE INTERVAL BASED ON THE LOG PEAK DESACETYLDILTIAZEM
 CONCENTRATION - LOG C_{max} (ng/mL)

Source	DF	TYPE III SS	Mean Square	F Value	Pr > F
ERROR	25	0.708654	0.028346	.	
sq	1	0.394468	0.394468	13.916121	0.000987
subj (sq)	25	14.202870	0.568115	20.042043	0.000000
peri	1	0.013757	0.013757	0.485319	0.492450
drug	1	0.039050	0.039050	1.377620	0.251568

INTRA-SUBJECT C.V. = $100 \times \text{SQRT}(\text{MSE}) = 100 \times \text{SQRT}(0.028346) = 16.84 \%$

DIFFERENCE = TEST - REFERENCE = $2.193378 - 2.247198 = -.053820$

SE DIFFERENCE = 0.045854

C_{max} RATIO = $100 \times e^{\frac{(\text{difference})}{\text{SE DIFFERENCE}}} = 100 \times e^{\frac{(2.193378 - 2.247198)}{0.045854}} = 94.76 \%$

90% GEOMETRIC CONFIDENCE INTERVAL

LOWER, UPPER = $100 \times e^{(\text{difference} \pm t_{0.05, 25} \times \text{SE difference})}$

LOWER = $100 \times e^{(-.053820 - 1.7081 \times 0.045854)} = 87.62 \%$

UPPER = $100 \times e^{(-.053820 + 1.7081 \times 0.045854)} = 102.48 \%$

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 15.

ANOVA ON DESACETYLDILTIAZEM T_{max}

The GLM Procedure

Dependent Variable: t_{max}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	839.012734	29.964741	4.34	0.0002
Error	25	172.588773	6.903551		
Corrected Total	53	1011.601507			

R-Square	Coeff Var	Root MSE	t _{max} Mean
0.829391	12.46756	2.627461	21.07438

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	12.3766980	12.3766980	1.79	0.1926
subj(sq)	25	710.3246703	28.4129868	4.12	0.0004
peri	1	62.3446942	62.3446942	9.03	0.0060
drug	1	58.2718547	58.2718547	8.44	0.0076

The GLM Procedure
 Least Squares Means

drug	t _{max} LSMEAN	Standard Error	Pr > t
A	20.0171245	0.5060023	<.0001
B	22.0961538	0.5060023	<.0001

sq	t _{max} LSMEAN	Standard Error	Pr > t
AB	20.5775641	0.5152875	<.0001
BA	21.5357143	0.4965434	<.0001

peri	t _{max} LSMEAN	Standard Error	Pr > t
1	19.9814103	0.5060023	<.0001
2	22.1318681	0.5060023	<.0001

The GLM Procedure

Dependent Variable: t_{max}

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	12.37669798	12.37669798	0.44	0.5153

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	-2.07902930	0.71559526	-2.91	0.0076

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 16.

THE APPARENT HALF-LIFE OF DESACETYLDILTIAZEM

SUBJECT No.	T _{1/2} (hrs.)	
	CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg
01	12.16	9.63
03	N.C.	16.72
04	25.56	17.07
05	10.68	8.22
06	27.20	14.12
07	10.46	10.23
08	10.07	9.32
09	9.72	9.93
10	10.38	9.58
11	10.11	11.82
12	9.46	11.07
13	15.39	11.89
14	11.51	11.68
15	14.04	11.62
16	15.73	26.58
17	9.13	9.43
18	9.94	10.78
19	9.17	11.90
20	8.85	10.19
21	10.15	12.87
22	12.53	12.88
23	17.04	15.07
24	14.34	14.87
25	10.75	10.23
26	9.24	8.82
27	10.49	13.14
28	15.87	10.65
MEAN	12.69	12.23
SD(±)	4.69	3.68
C.V.(%)	36.93	30.08
Range (Min.)	8.85	8.22
(Max.)	27.20	26.58
Num of subjects	26	27

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 17.

ANOVA ON DESACETYLDILTIAZEM HALF-LIFE

The GLM Procedure

NOTE: Due to missing values, only 53 observations can be used in this analysis.

The GLM Procedure

Dependent Variable: t_{half}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	689.8227650	24.6365273	2.76	0.0068
Error	24	214.1511529	8.9229647		
Corrected Total	52	903.9739179			

R-Square	Coeff Var	Root MSE	t_{half} Mean
0.763100	23.97724	2.987133	12.45820

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	79.4380635	79.4380635	8.90	0.0065
subj(sq)	25	578.7707399	23.1508296	2.59	0.0112
peri	1	7.9068225	7.9068225	0.89	0.3559
drug	1	4.2031288	4.2031288	0.47	0.4991

The GLM Procedure
 Least Squares Means

drug	t_{half} LSMEAN	Standard Error	Pr > t
A	12.7723520	0.5996110	<.0001
B	12.2020520	0.5752687	<.0001

sq	t_{half} LSMEAN	Standard Error	Pr > t
AB	11.2475455	0.6097460	<.0001
BA	13.7268585	0.5645151	<.0001

peri	t_{half} LSMEAN	Standard Error	Pr > t
1	12.0961018	0.5996110	<.0001
2	12.8783022	0.5752687	<.0001

The GLM Procedure

Dependent Variable: t_{half}

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	79.43806346	79.43806346	3.43	0.0758

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	0.57030002	0.83094374	0.69	0.4991

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 18.

THE ELIMINATION RATE CONSTANT OF DESACETYLDILTIAZEM

SUBJECT No.	K_{e1} (hour ⁻¹)	
	CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg
01	0.057	0.072
03	N.C.	0.041
04	0.027	0.041
05	0.065	0.084
06	0.025	0.049
07	0.066	0.068
08	0.069	0.074
09	0.071	0.070
10	0.067	0.072
11	0.069	0.059
12	0.073	0.063
13	0.045	0.058
14	0.060	0.059
15	0.049	0.060
16	0.044	0.026
17	0.076	0.073
18	0.070	0.064
19	0.076	0.058
20	0.078	0.068
21	0.068	0.054
22	0.055	0.054
23	0.041	0.046
24	0.048	0.047
25	0.064	0.068
26	0.075	0.079
27	0.066	0.053
28	0.044	0.065
MEAN	0.060	0.060
SD(±)	0.015	0.013
C.V.(%)	24.898	21.747
Range (Min.)	0.025	0.026
(Max.)	0.078	0.084
Num of subjects	26	27

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 18. (Cont'd)

CRITERIA USED TO DETECT 'NO CALCULATION' (NC) OF K_{e1} ($K_{e1} = .$)
 Compound: DESACETYLDILTIAZEM

Treatment Previous group Concentration (f)	Subject Number Reason	r-value (a)	Estimated K_{e1} (b)	The Max Concen in linear range (c)	C_{max} Concentration (d)	Last Concentration (e)
A 5.556	03 4	0.9683	-0.0506	16.237	16.523	5.579

CRITERIA:

1. Poor linearity: Terminal linear range can not be detected with $r \geq 0.95$ (a)
2. Terminal linear range increases in concentration (positive slope), $K_{e1} \geq 0$ (b)
3. Terminal linear range contains C_{max} (c), (d)
4. Sudden increase in last concentration (Last concentration > Previous Concentration (e), (f))

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
Study # 2443 (B01-527PK-DILG12)
TABLE 2. 19.

ANOVA ON DESACETYLDILTIAZEM k_{e1}

The GLM Procedure

NOTE: Due to missing values, only 53 observations can be used in this analysis.

The GLM Procedure

Dependent Variable: k_{e1}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	0.00829626	0.00029629	4.27	0.0003
Error	24	0.00166637	0.00006943		
Corrected Total	52	0.00996262			

R-Square	Coeff Var	Root MSE	k_{e1} Mean
0.832738	13.91196	0.008333	0.059895

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.00070141	0.00070141	10.10	0.0040
subj (sq)	25	0.00724144	0.00028966	4.17	0.0004
peri	1	0.00009371	0.00009371	1.35	0.2568
drug	1	0.00001557	0.00001557	0.22	0.6400

The GLM Procedure
Least Squares Means

drug	k_{e1} LSMEAN	Standard Error	Pr > t
A	0.05917097	0.00167261	<.0001
B	0.06026879	0.00160471	<.0001

sq	k_{e1} LSMEAN	Standard Error	Pr > t
AB	0.06340347	0.00170088	<.0001
BA	0.05603629	0.00157471	<.0001

peri	k_{e1} LSMEAN	Standard Error	Pr > t
1	0.06106632	0.00167261	<.0001
2	0.05837344	0.00160471	<.0001

The GLM Procedure

Dependent Variable: k_{e1}

Tests of Hypotheses Using the Type III MS for subj (sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.00070141	0.00070141	2.42	0.1323

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	-0.00109781	0.00231791	-0.47	0.6400

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 2. 20.

THE CORRELATION COEFFICIENT (r value) OF THE MOST LINEAR PORTION
 OF THE TERMINAL ELIMINATION PHASE FOR PLASMA DESACETYLDILTIAZEM

SUBJECT No.	CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg
01	0.99804	0.99253
03	N.C.	0.99650
04	0.98735	0.99897
05	0.99973	0.99683
06	0.98652	0.99910
07	0.99723	0.99597
08	0.95419	0.99412
09	0.99832	0.99982
10	0.97804	0.99924
11	0.99254	0.99056
12	0.99089	0.99975
13	0.98839	0.96864
14	0.99853	0.99680
15	0.99461	0.99659
16	0.99952	0.99299
17	0.99728	0.99114
18	0.99944	0.99508
19	0.99470	0.98673
20	0.99770	0.99356
21	0.98399	0.98562
22	0.95728	0.99671
23	0.98672	0.99241
24	0.99880	0.97885
25	0.99770	0.99989
26	0.99720	0.99915
27	0.99913	0.99437
28	0.98878	0.99192
MEAN	0.99087	0.99347
SD(±)	0.01186	0.00698
C.V.(%)	1.19662	0.70238
Range (Min.)	0.95419	0.96864
(Max.)	0.99973	0.99989
Num of subjects	26	27

N.C. = No Calculation of K_{e1}

FIGURES

MEAN PLASMA DESACETYLDILTIAZEM CONCENTRATIONS

STUDY # 2443 (N=27)

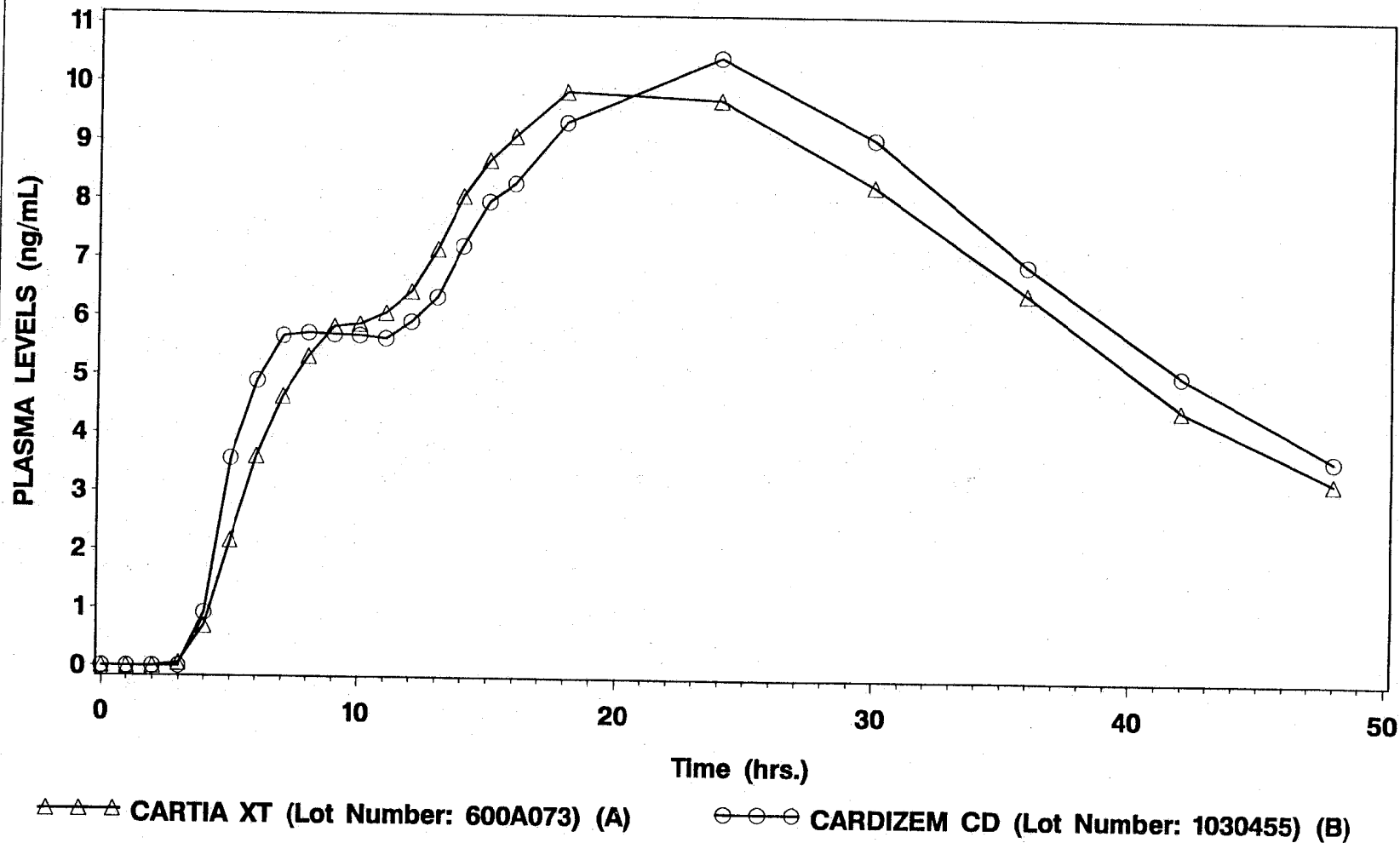


FIGURE 2.1

SEMI LOG MEAN PLASMA DESACETYLDILTIAZEM CONCENTRATIONS

STUDY # 2443 (N=27)

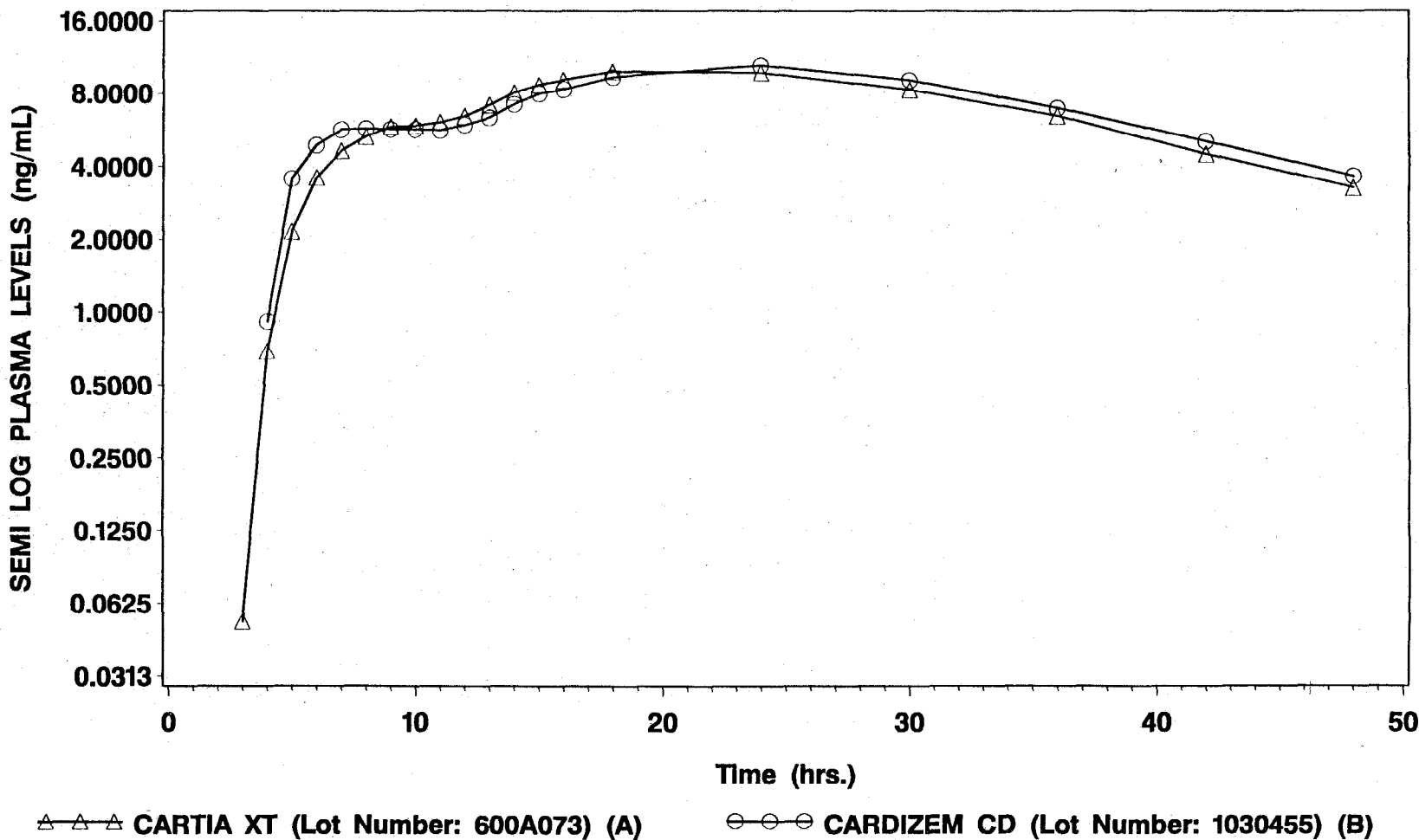


FIGURE 2.2

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 01

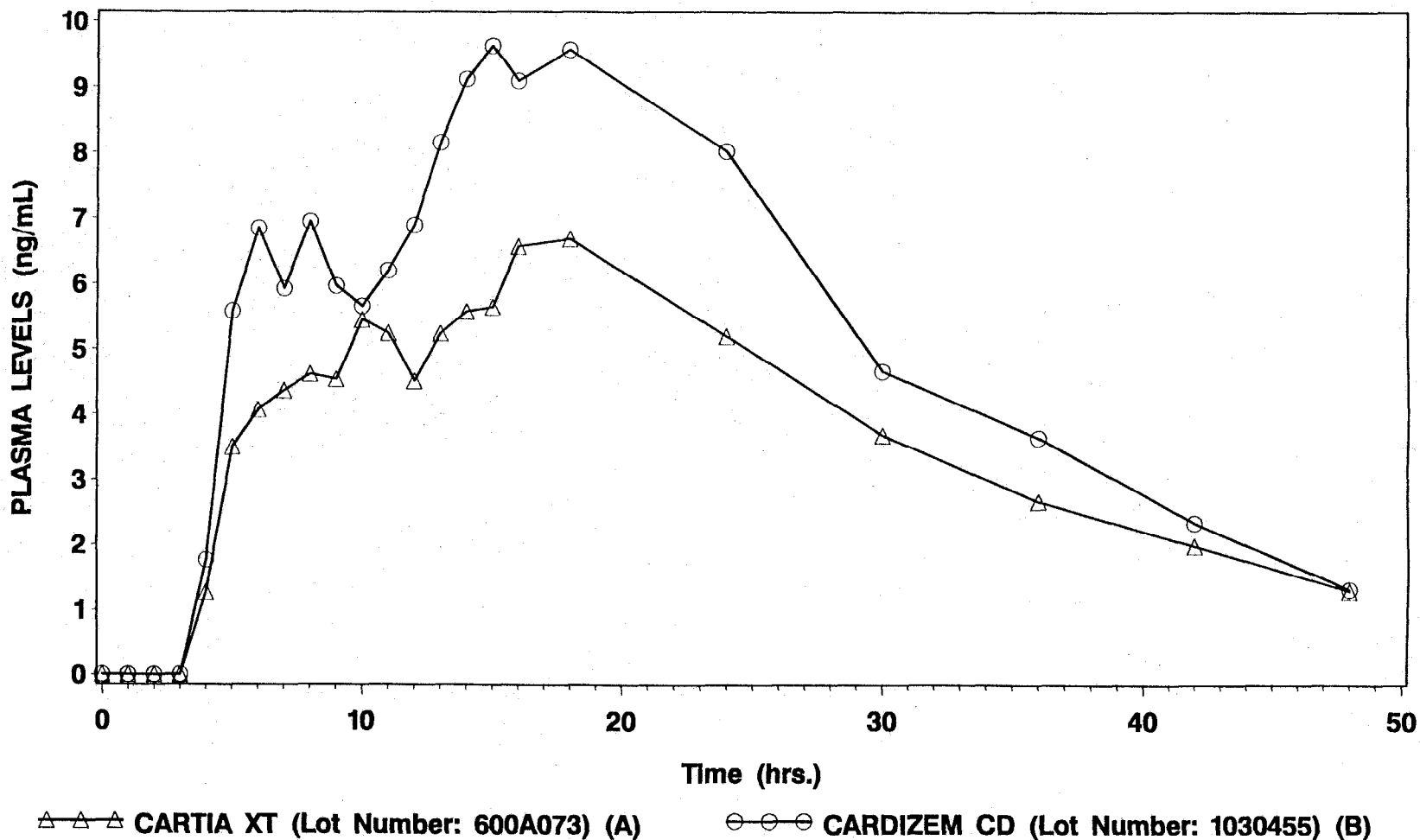


FIGURE 2.3

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 03

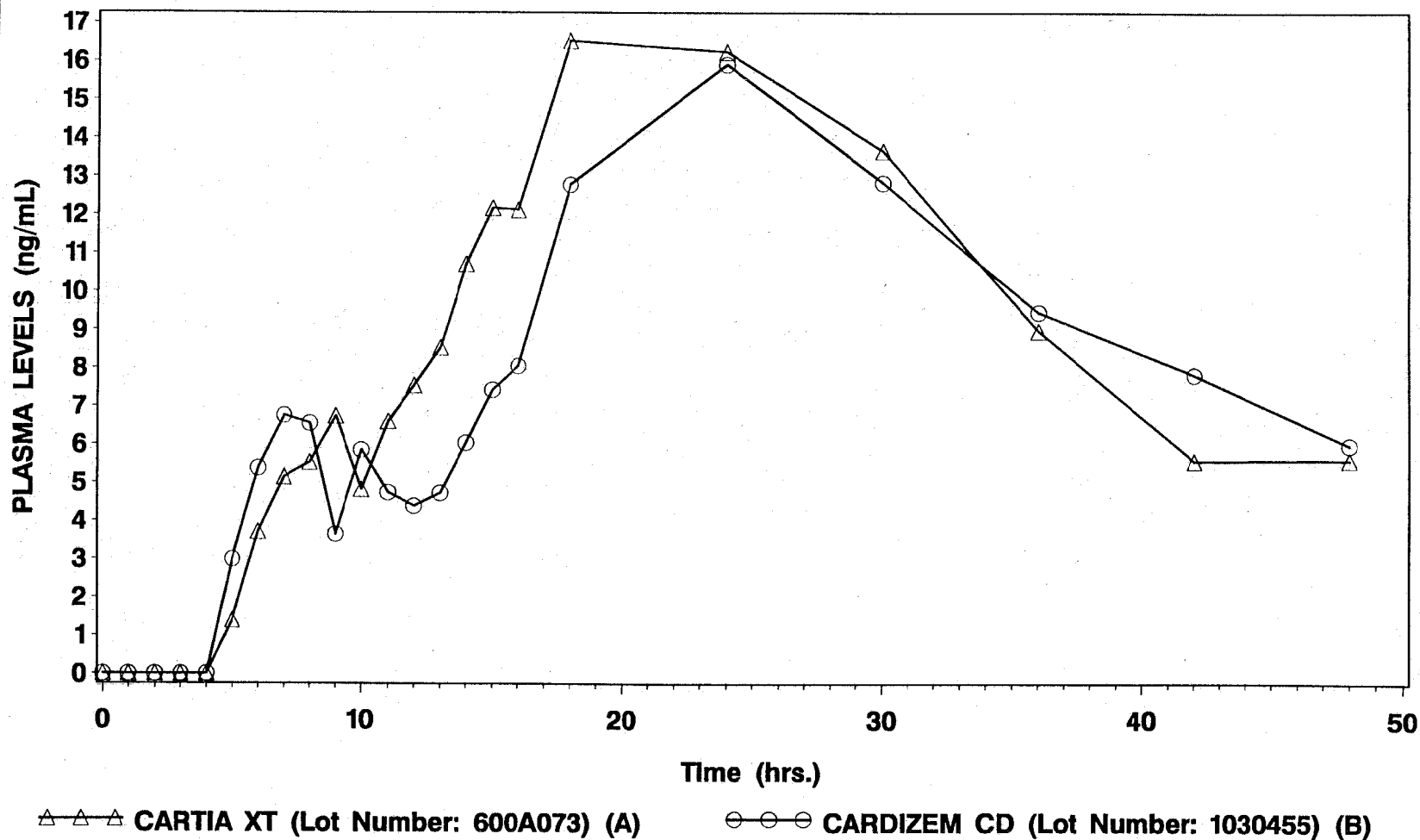
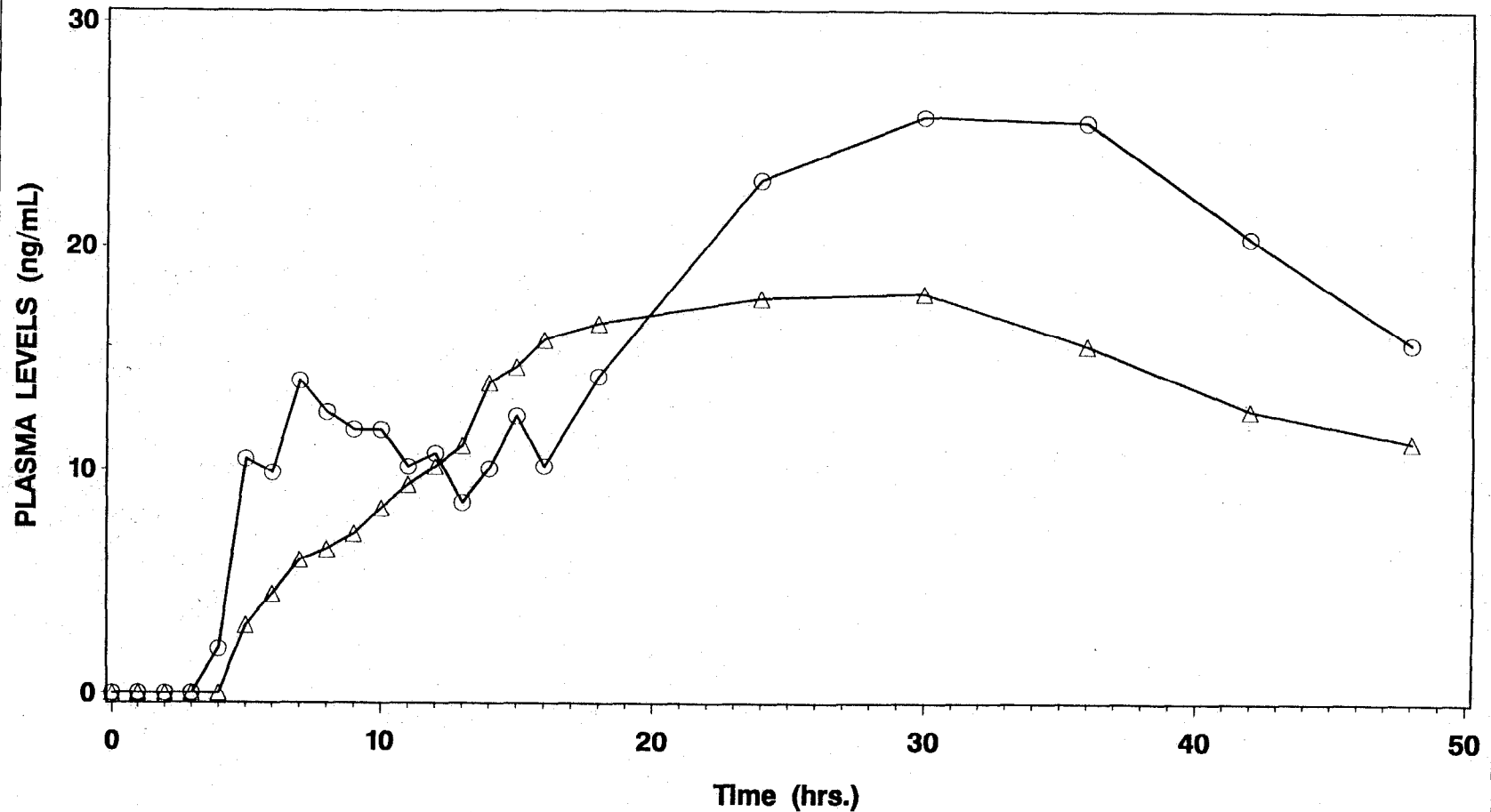


FIGURE 2.4

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 04



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 2.5

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 05

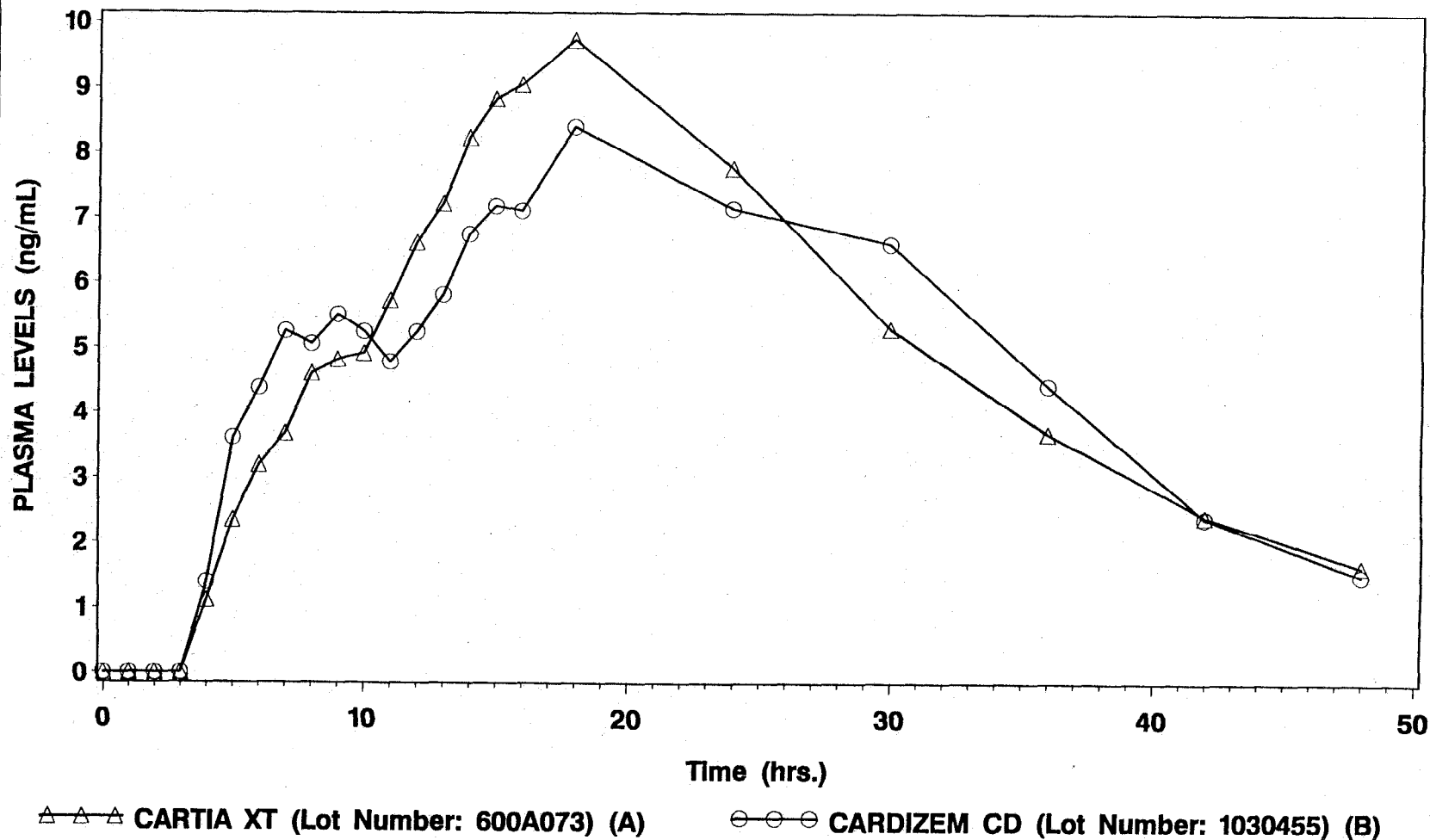


FIGURE 2.6

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 06

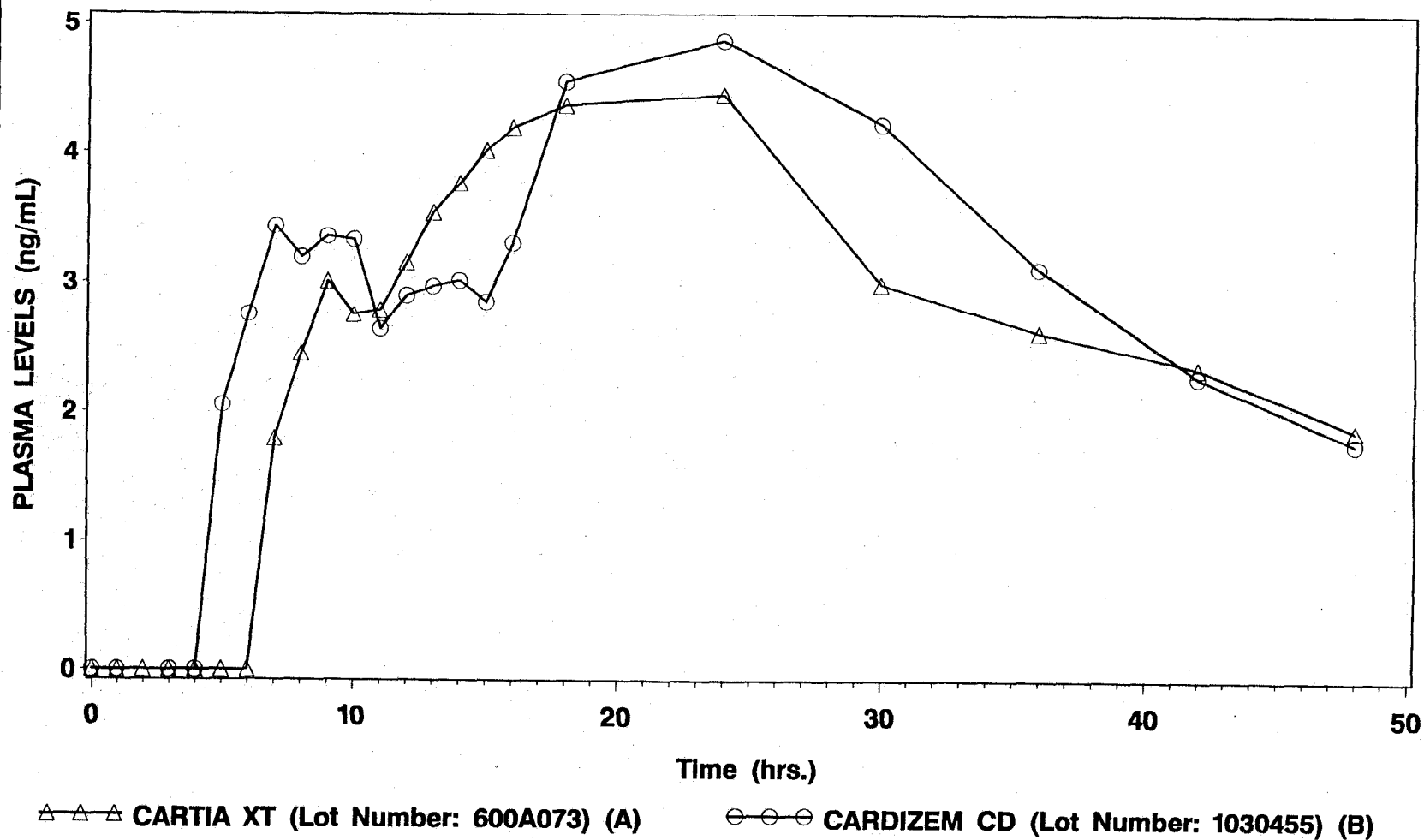


FIGURE 2.7

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 07

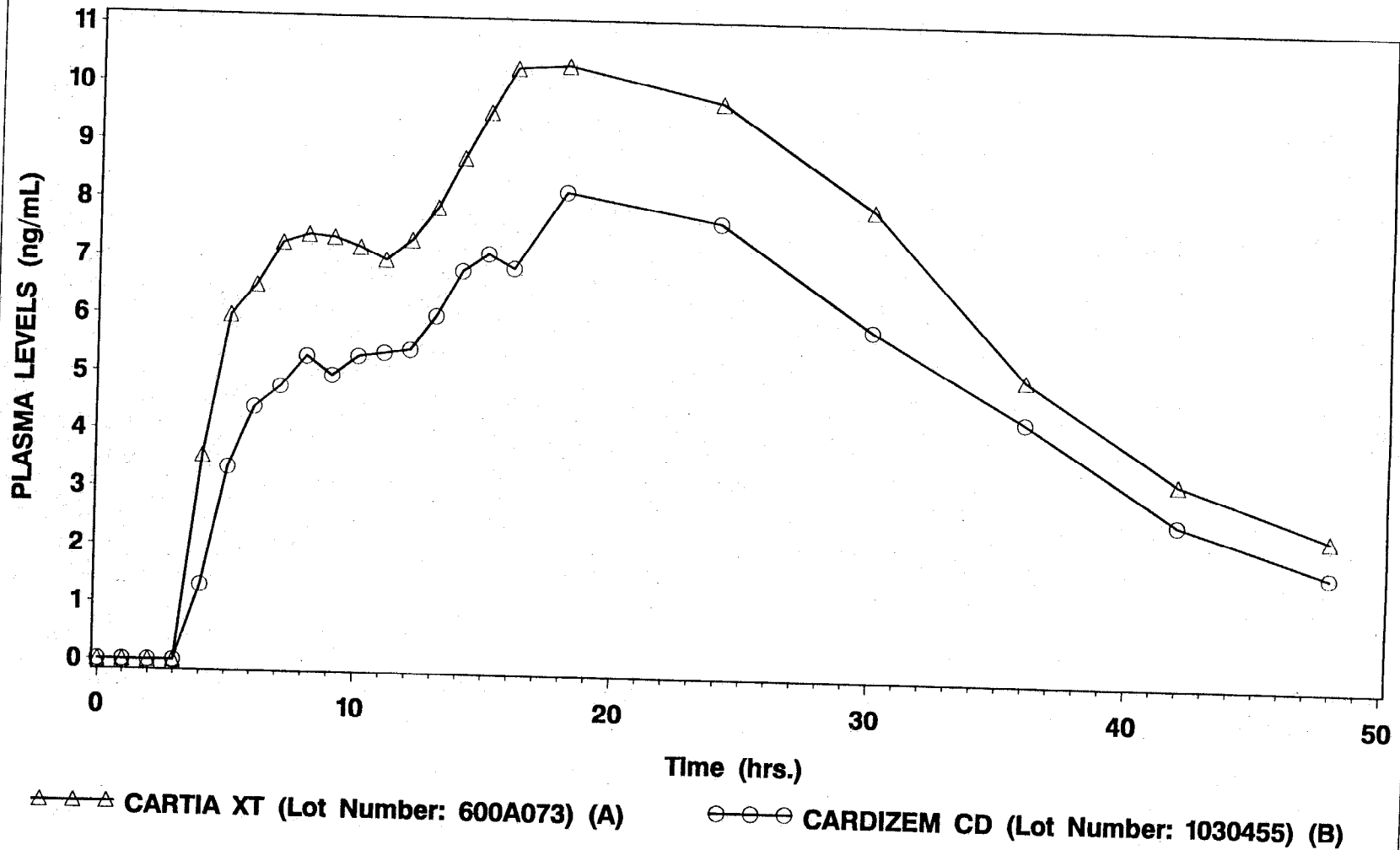


FIGURE 2.8

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 08

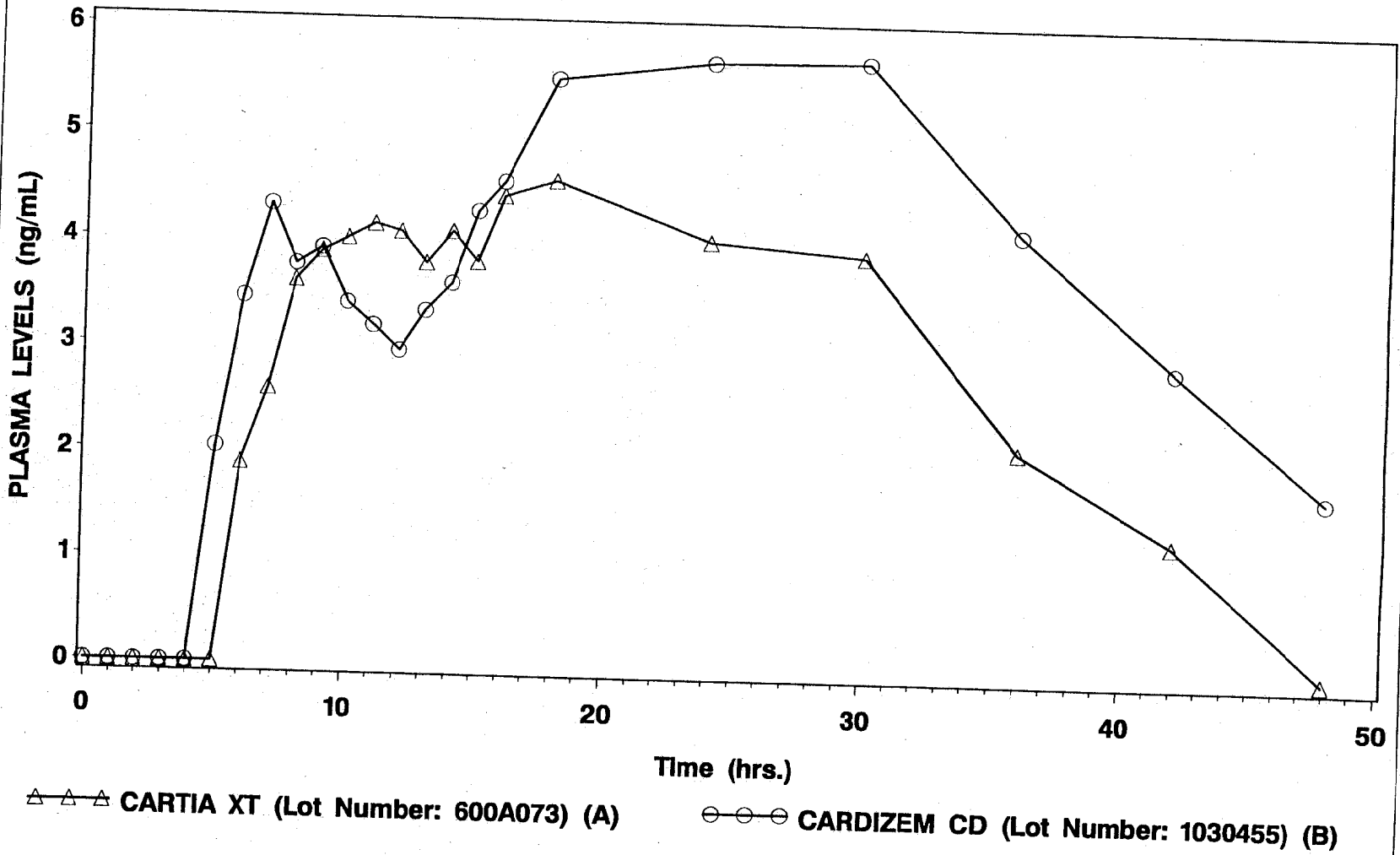


FIGURE 2.9

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 09

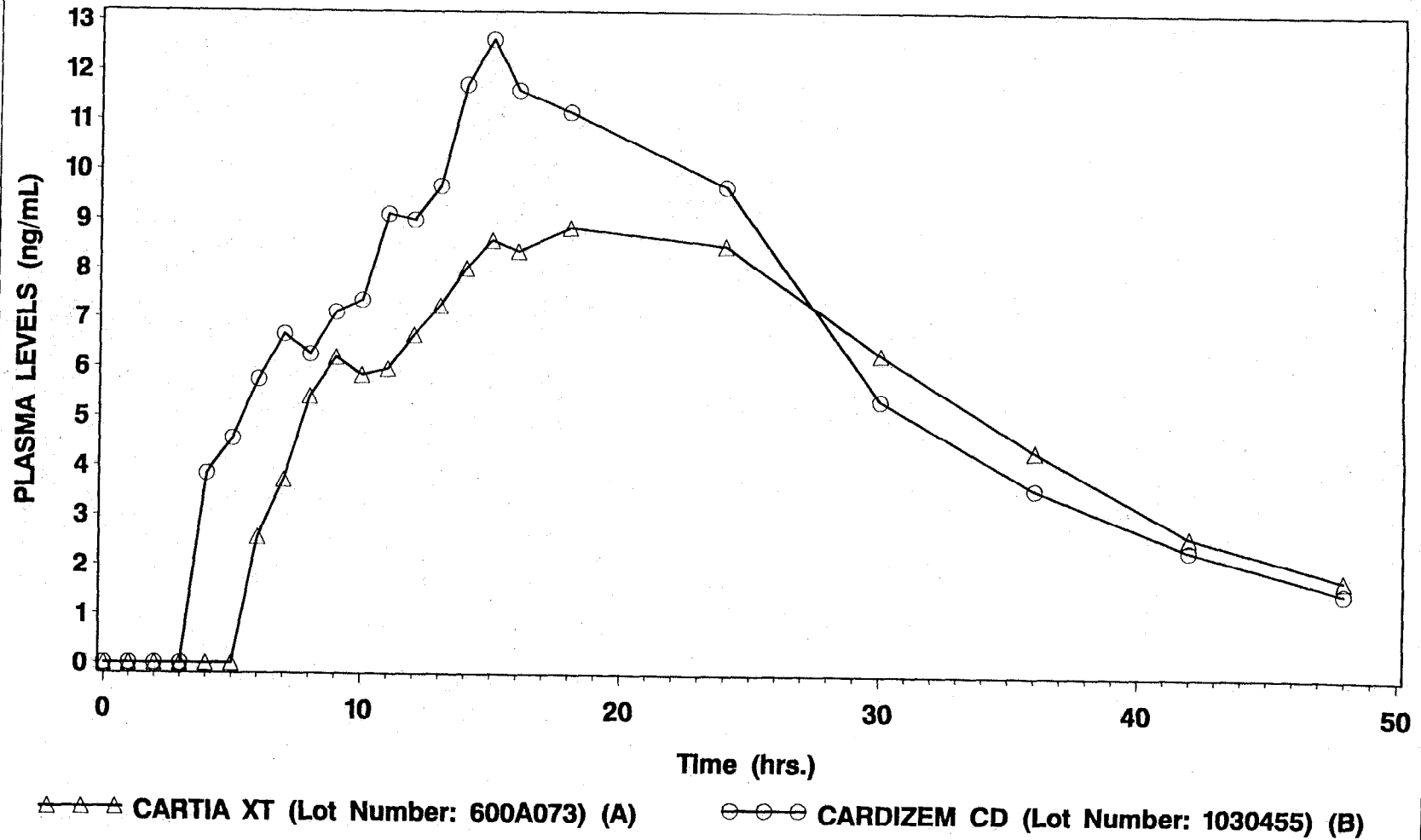


FIGURE 2.10

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 10

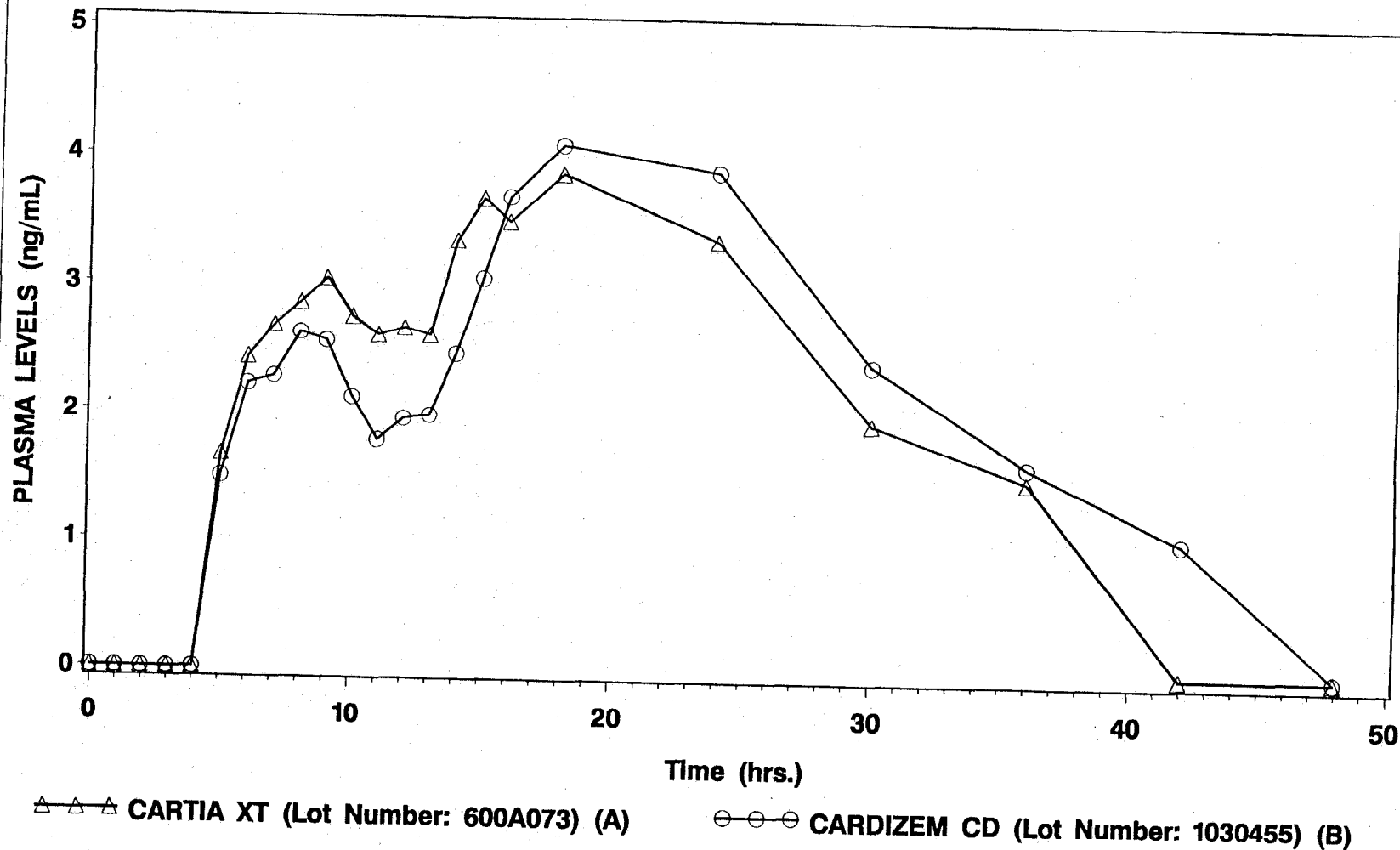


FIGURE 2.11

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 11

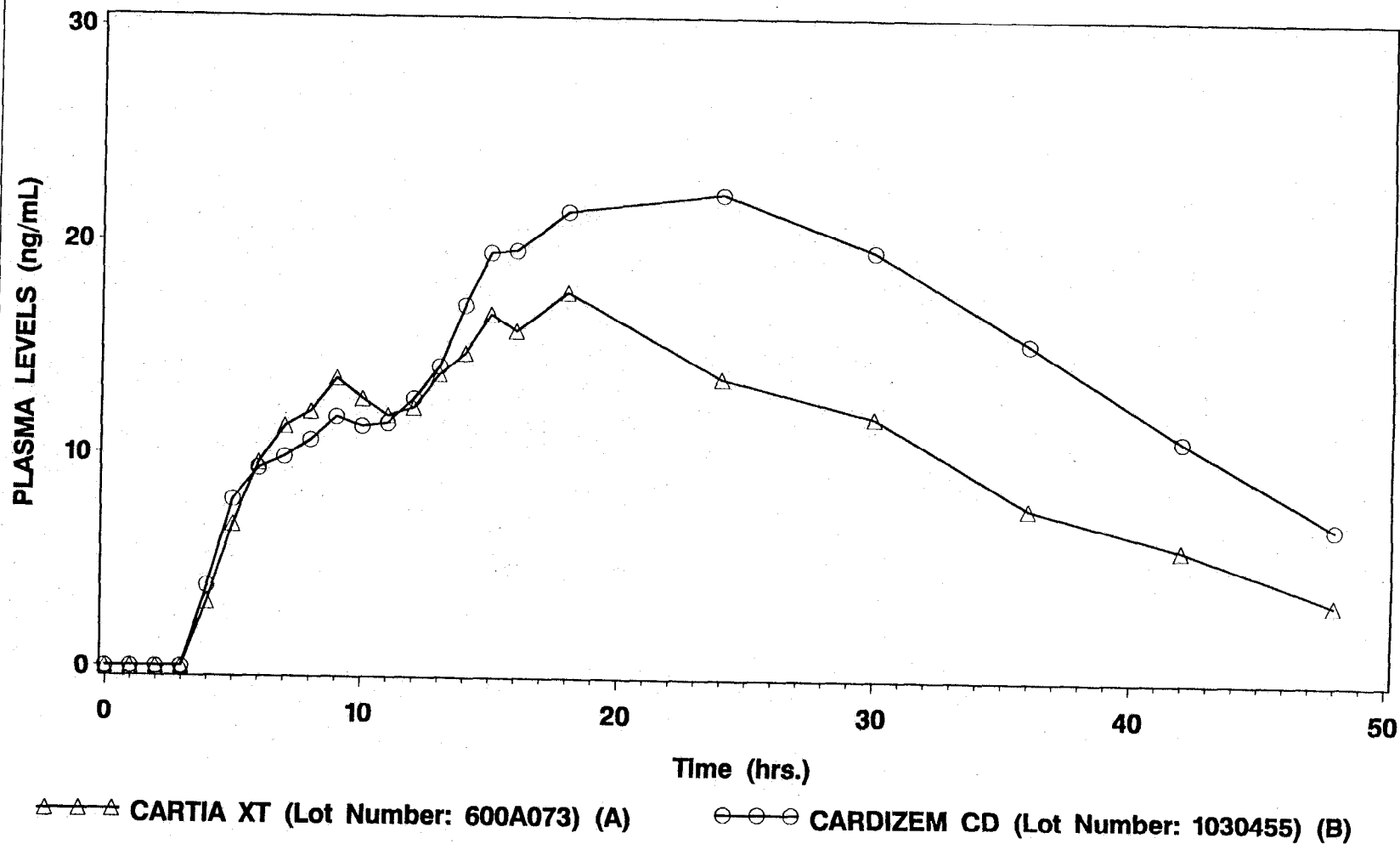


FIGURE 2.12

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 12

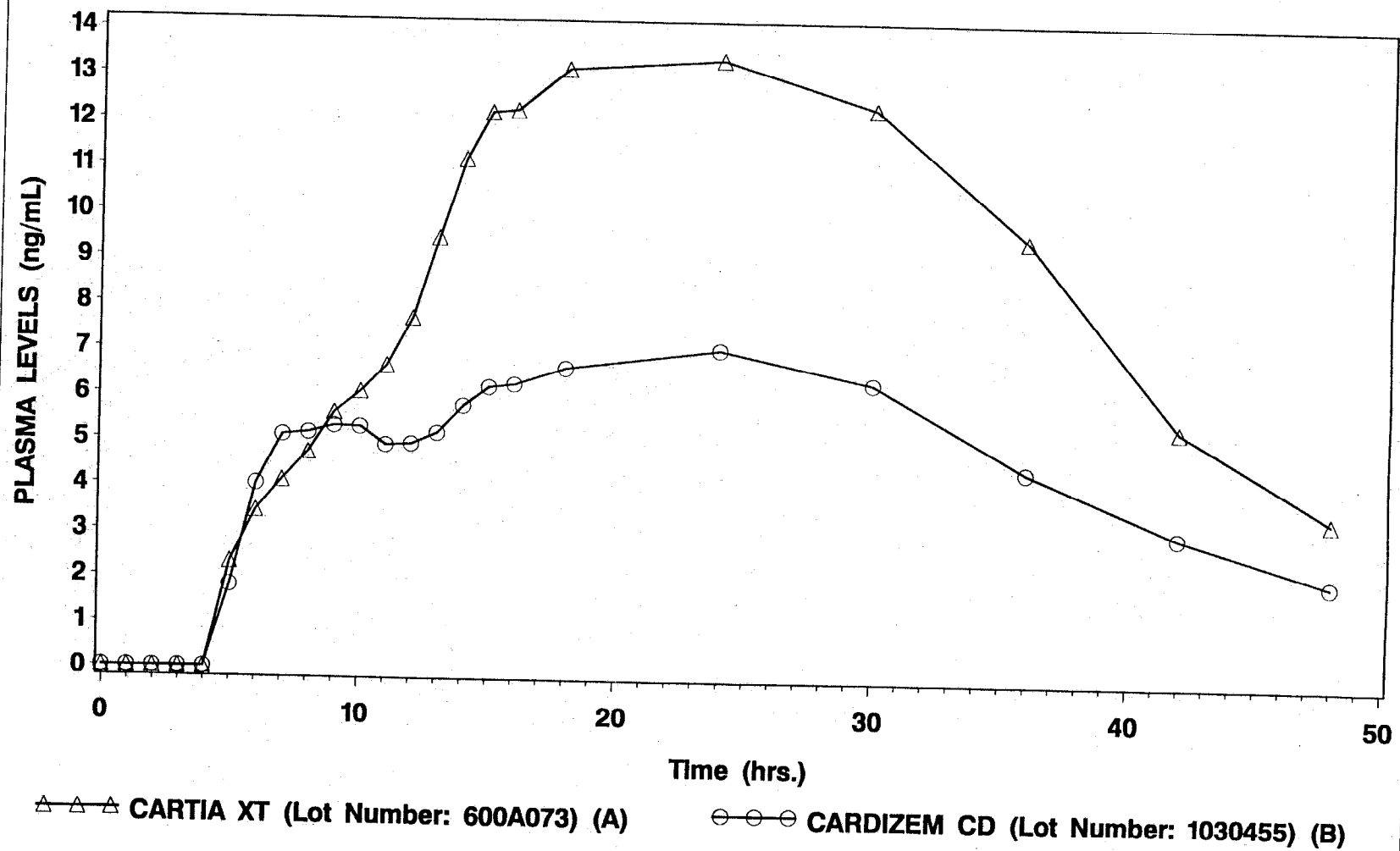


FIGURE 2.13

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 13

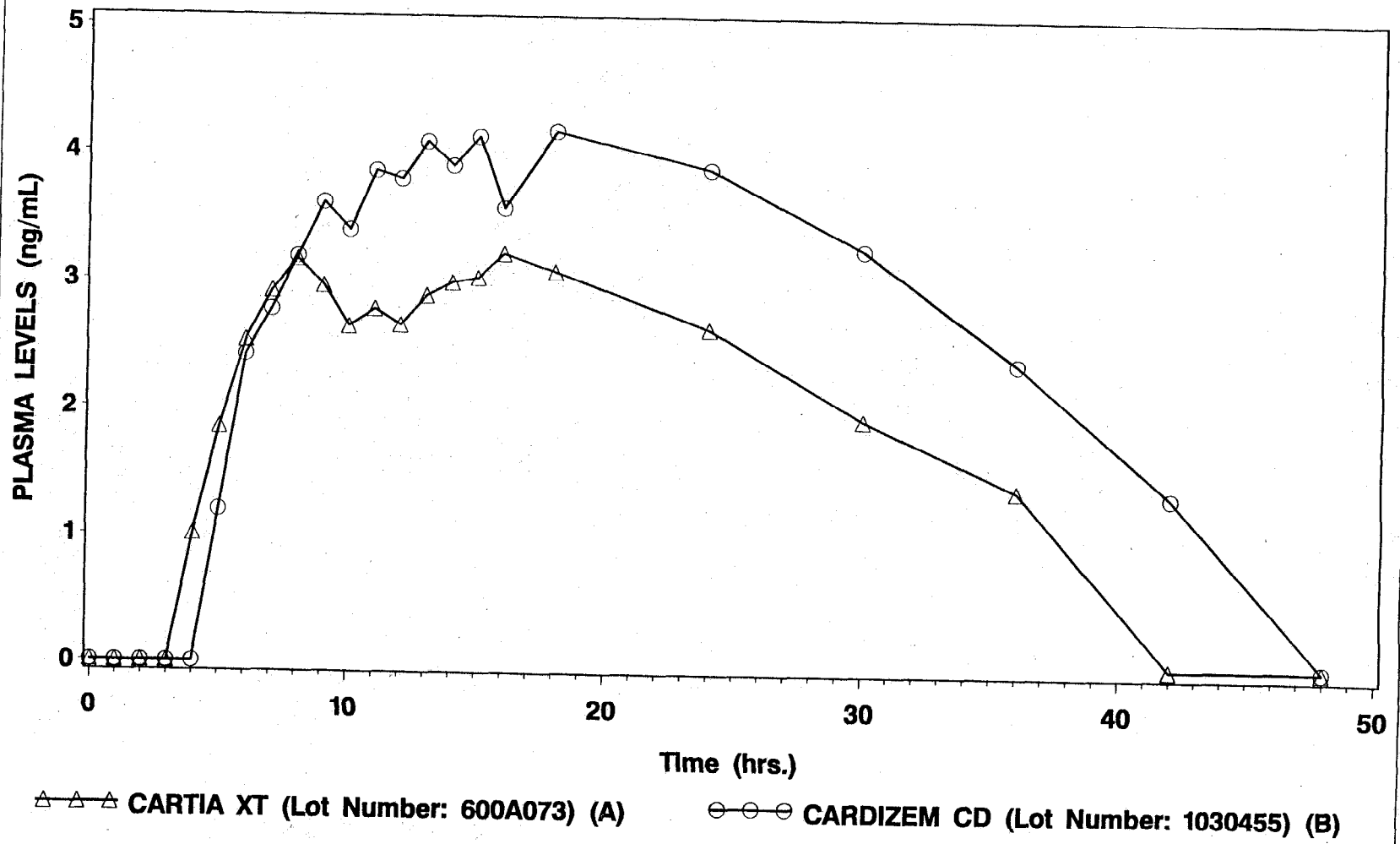


FIGURE 2.14

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 14

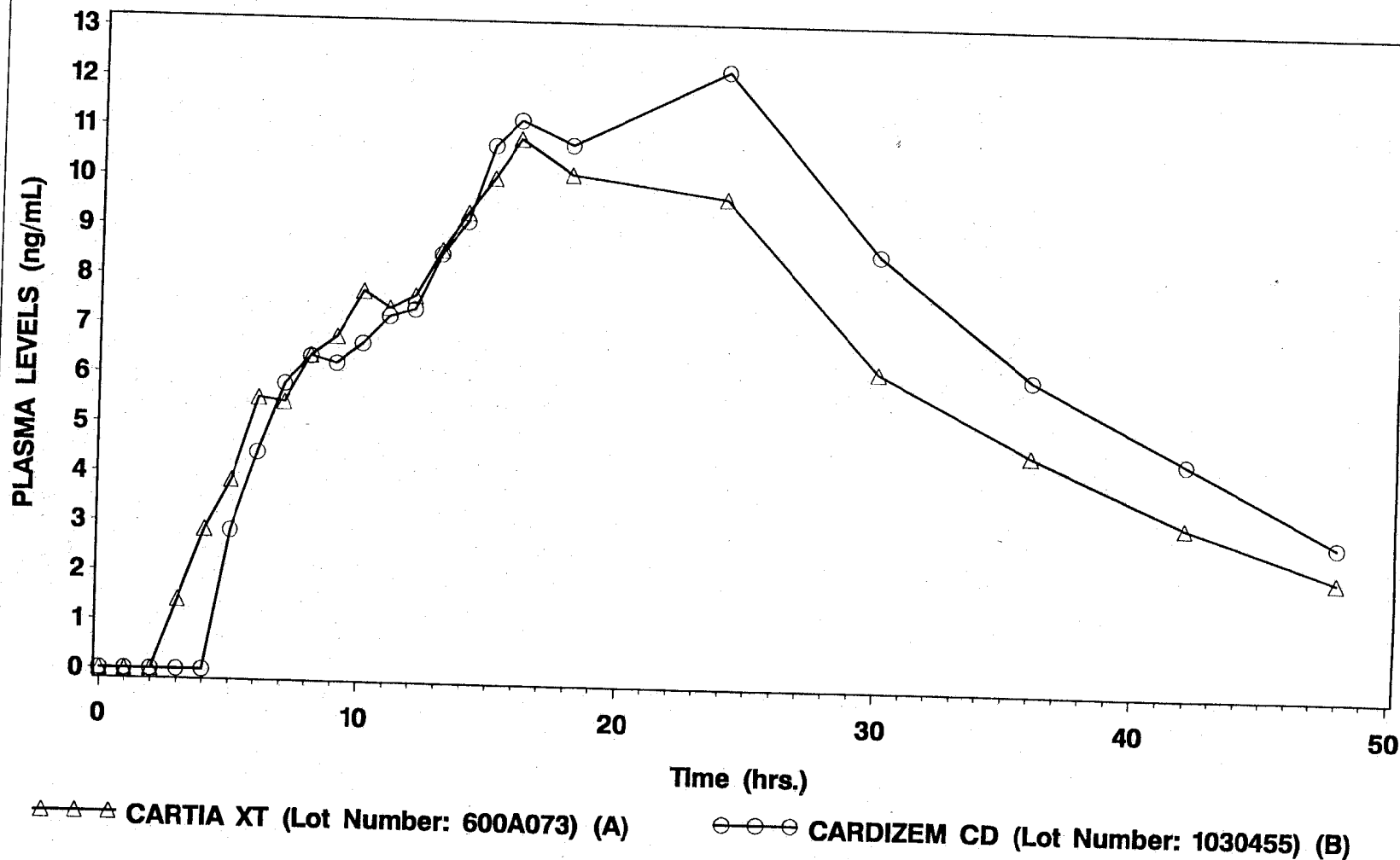


FIGURE 2.15

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 15

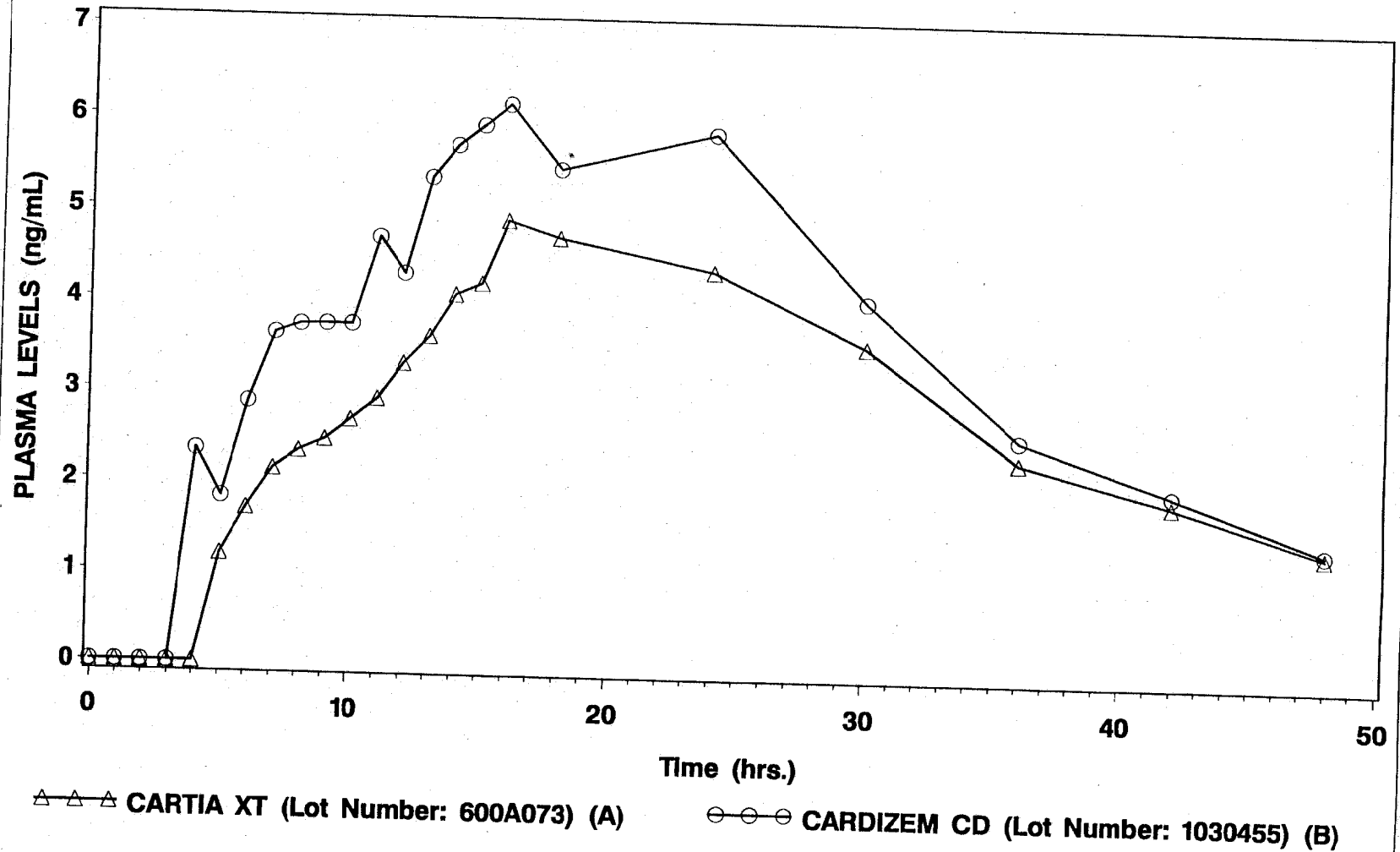


FIGURE 2.16

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 16

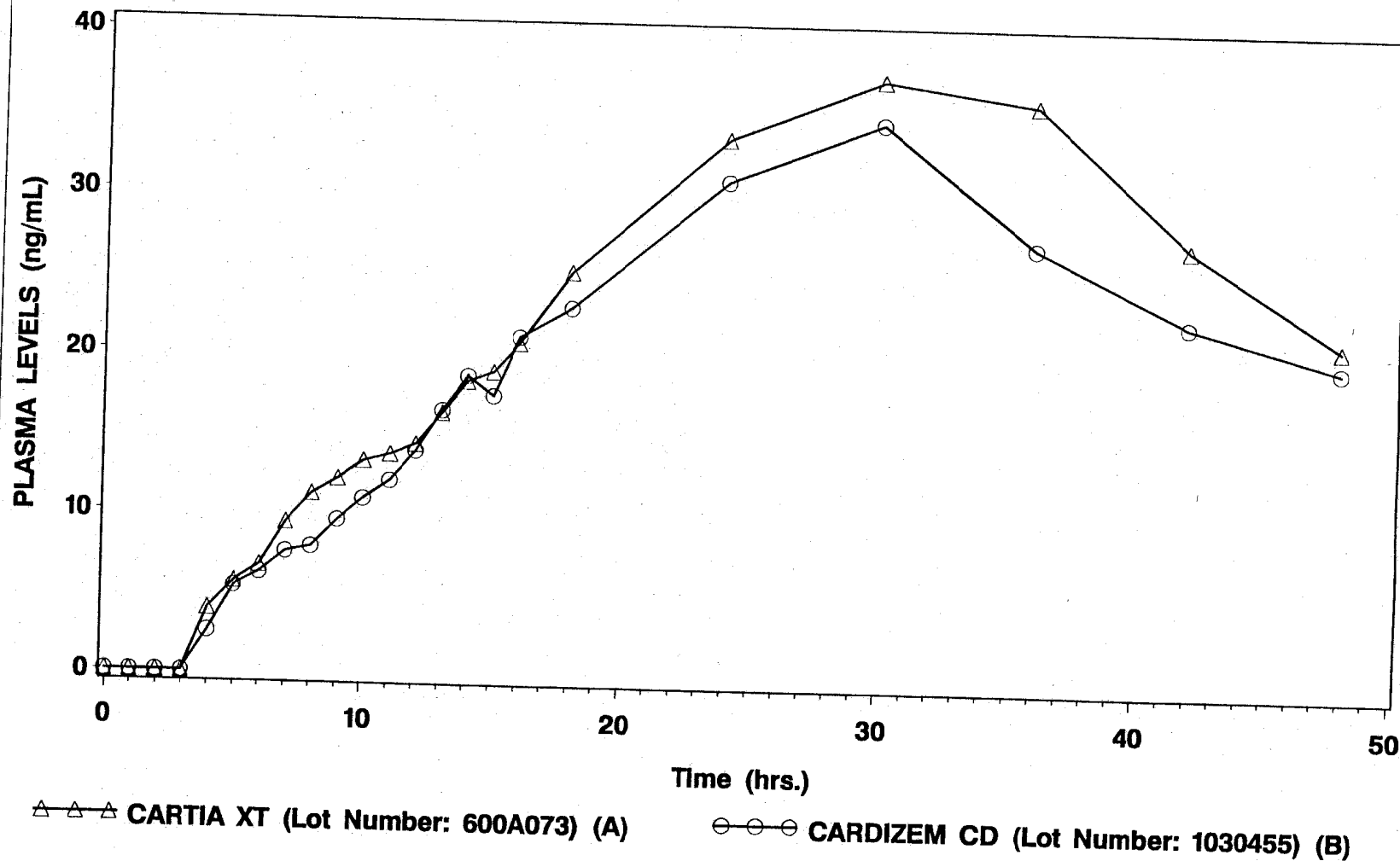


FIGURE 2.17

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 17

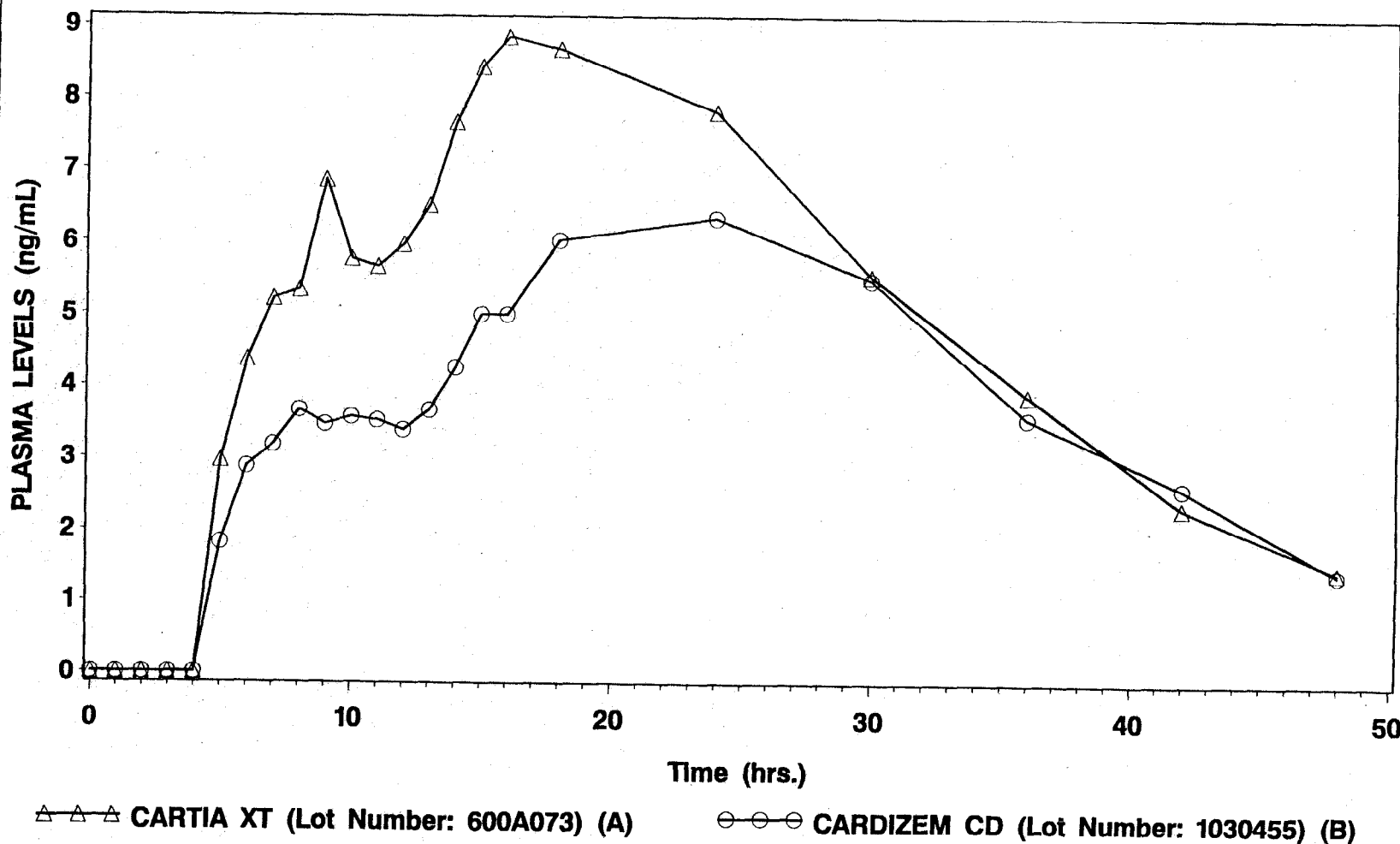


FIGURE 2.18

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 18

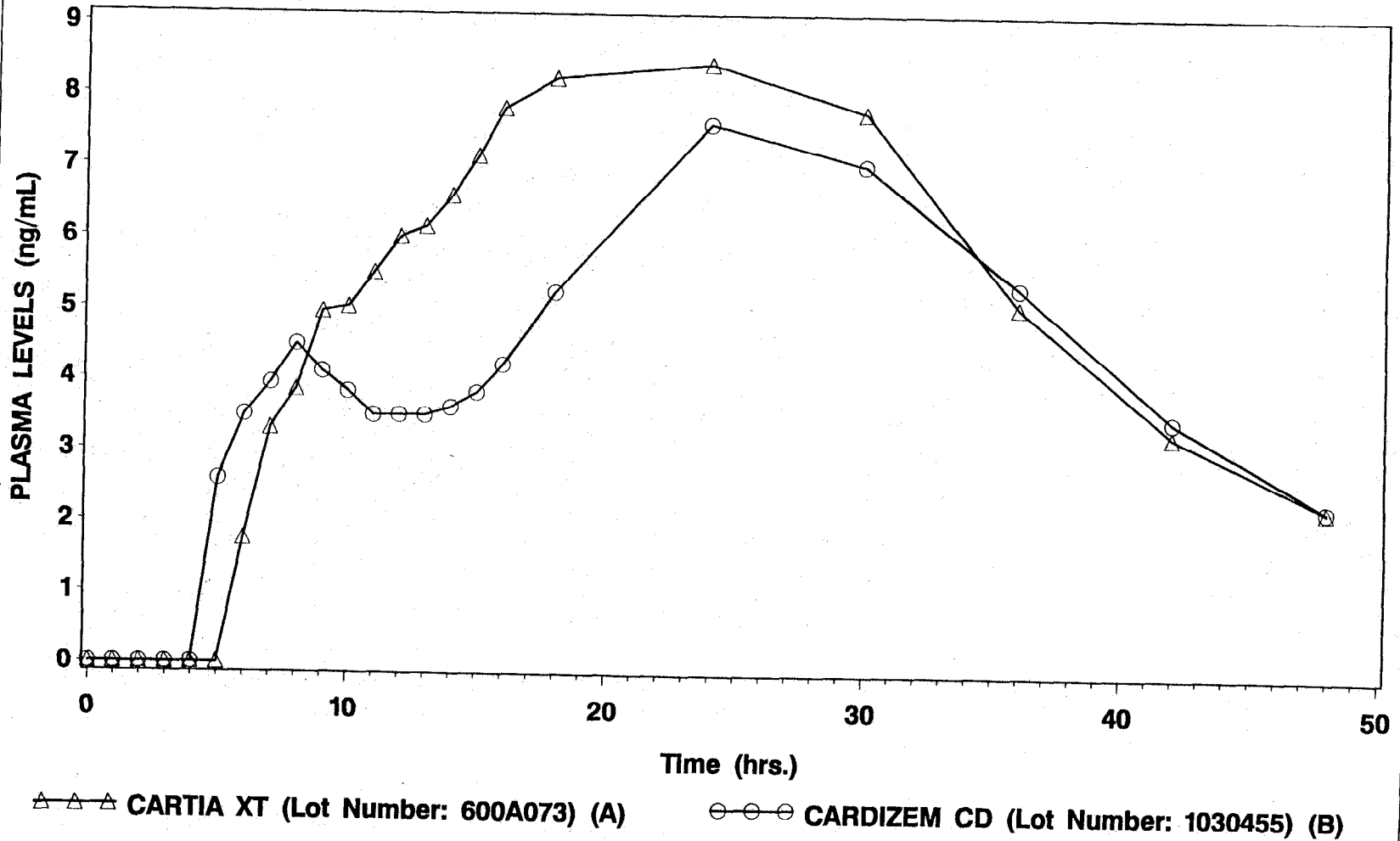


FIGURE 2.19

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 19

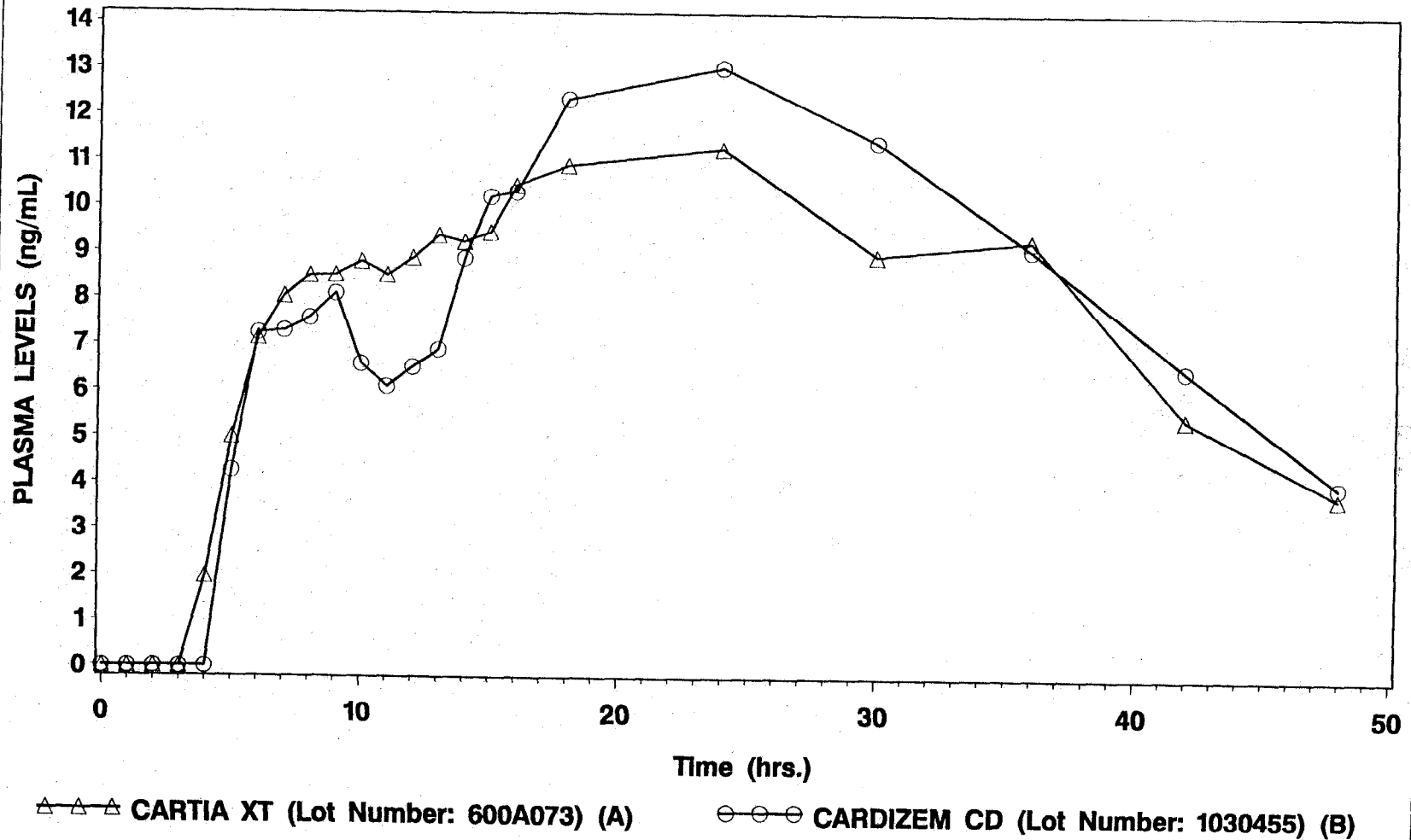


FIGURE 2.20

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 20

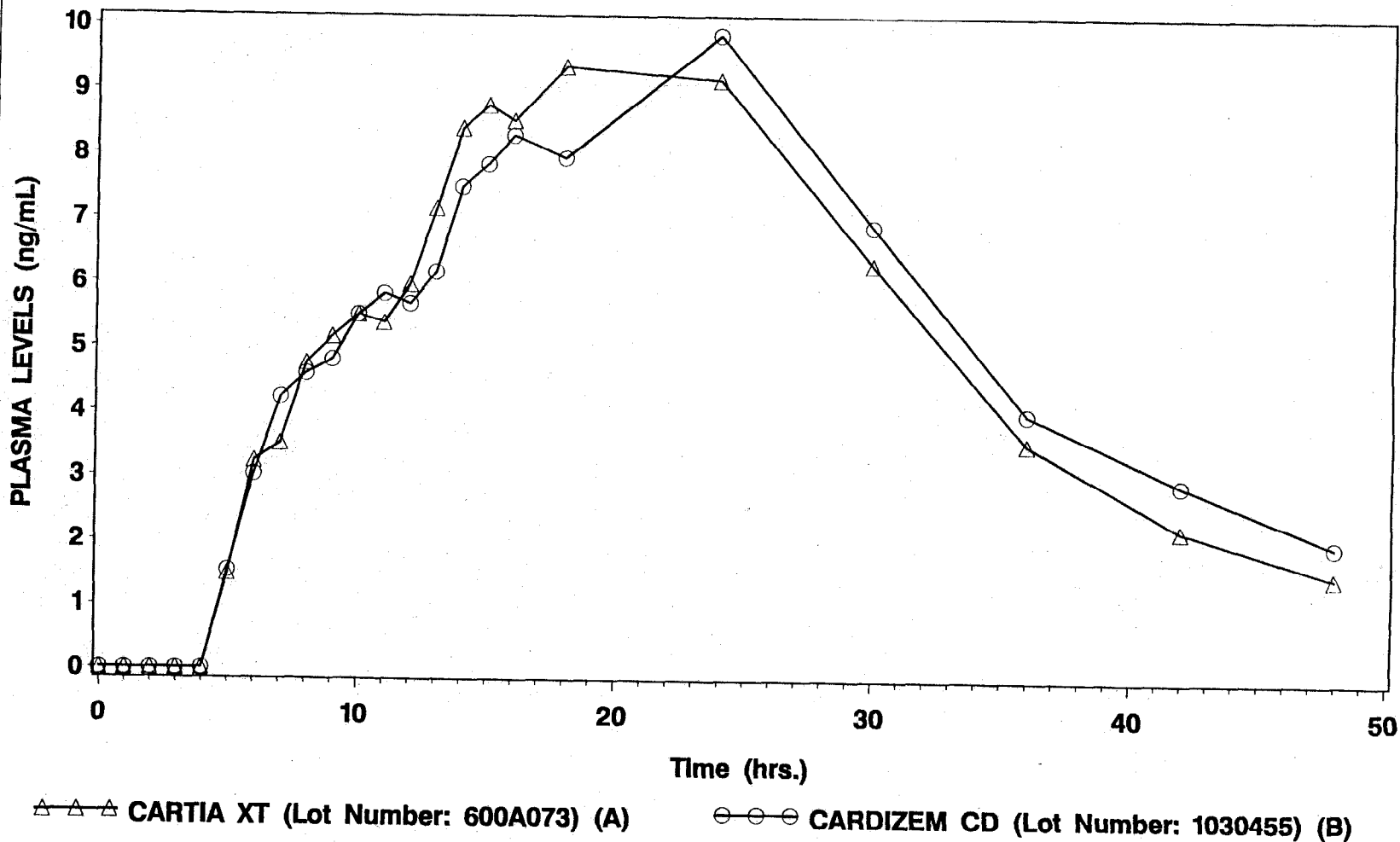


FIGURE 2.21

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 21

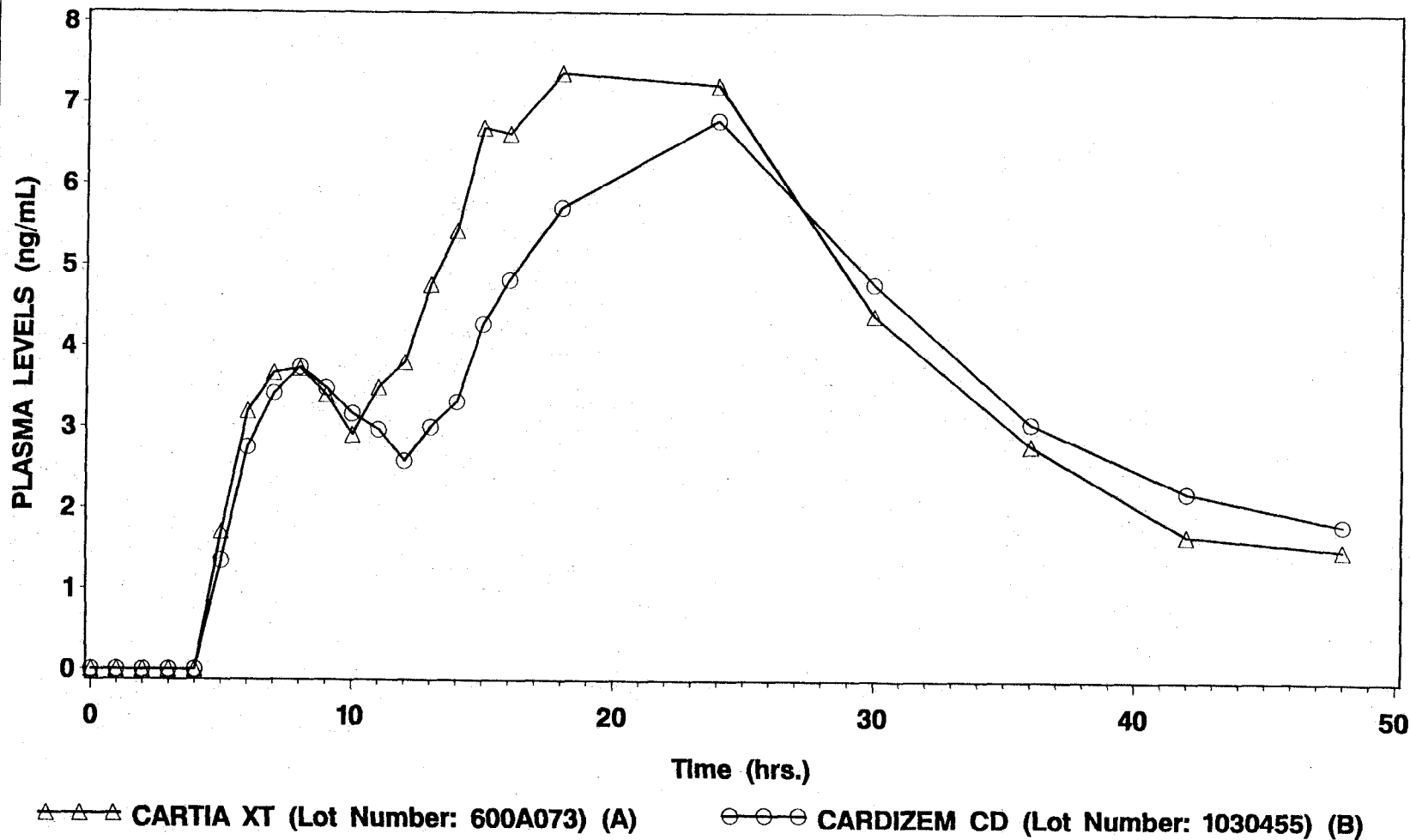


FIGURE 2.22

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 22

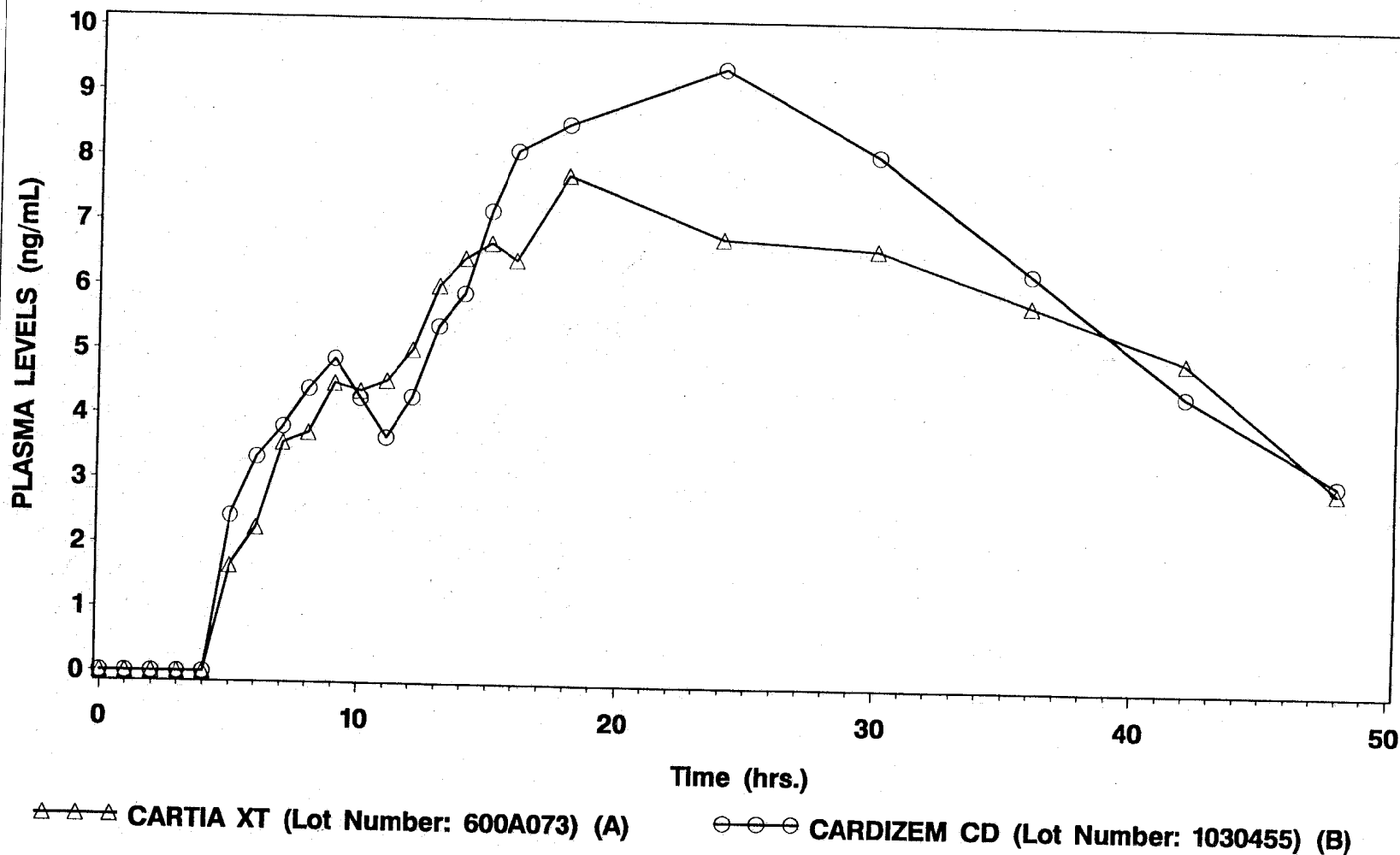


FIGURE 2.23

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 23

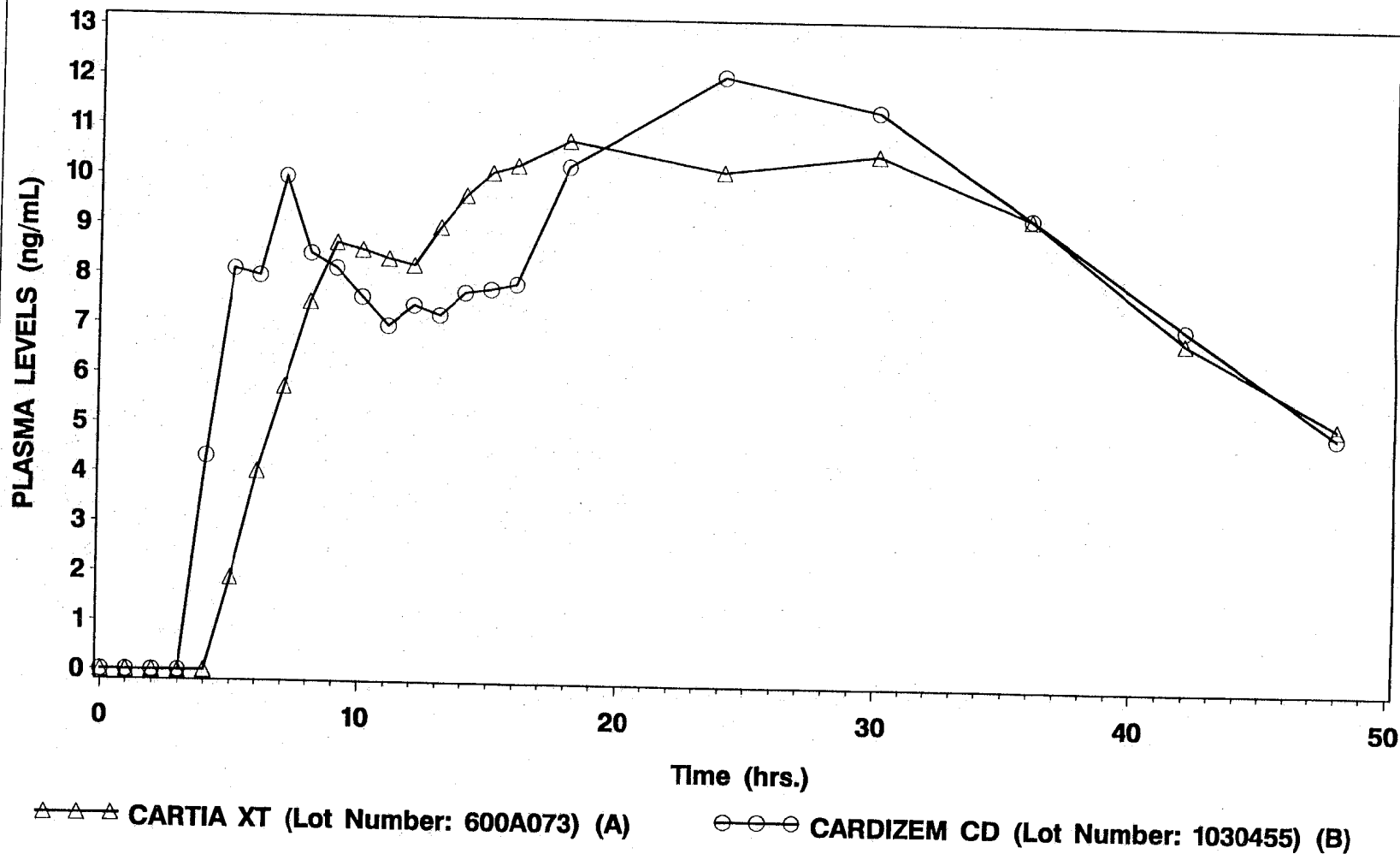


FIGURE 2.24

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 24

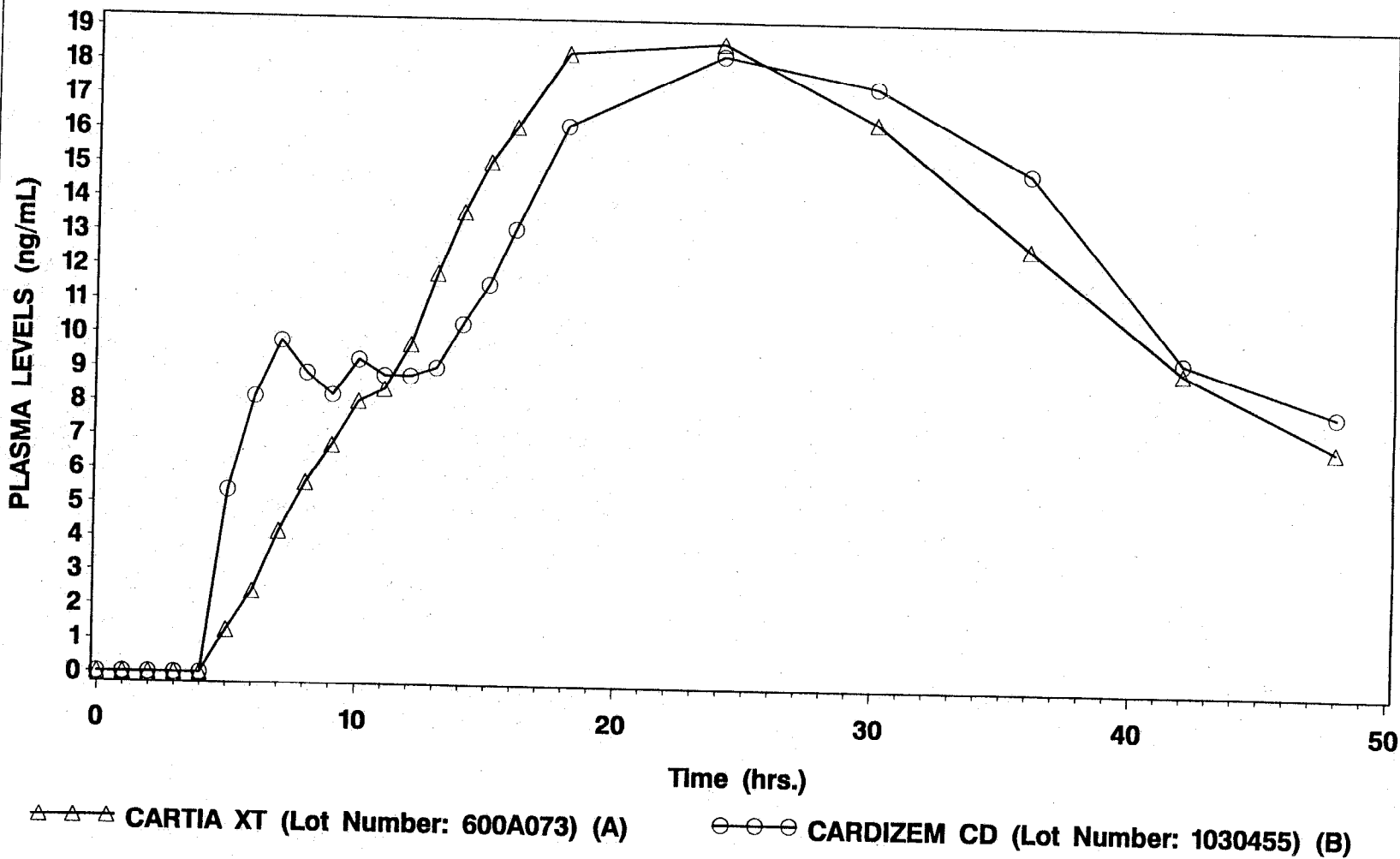


FIGURE 2.25

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 25

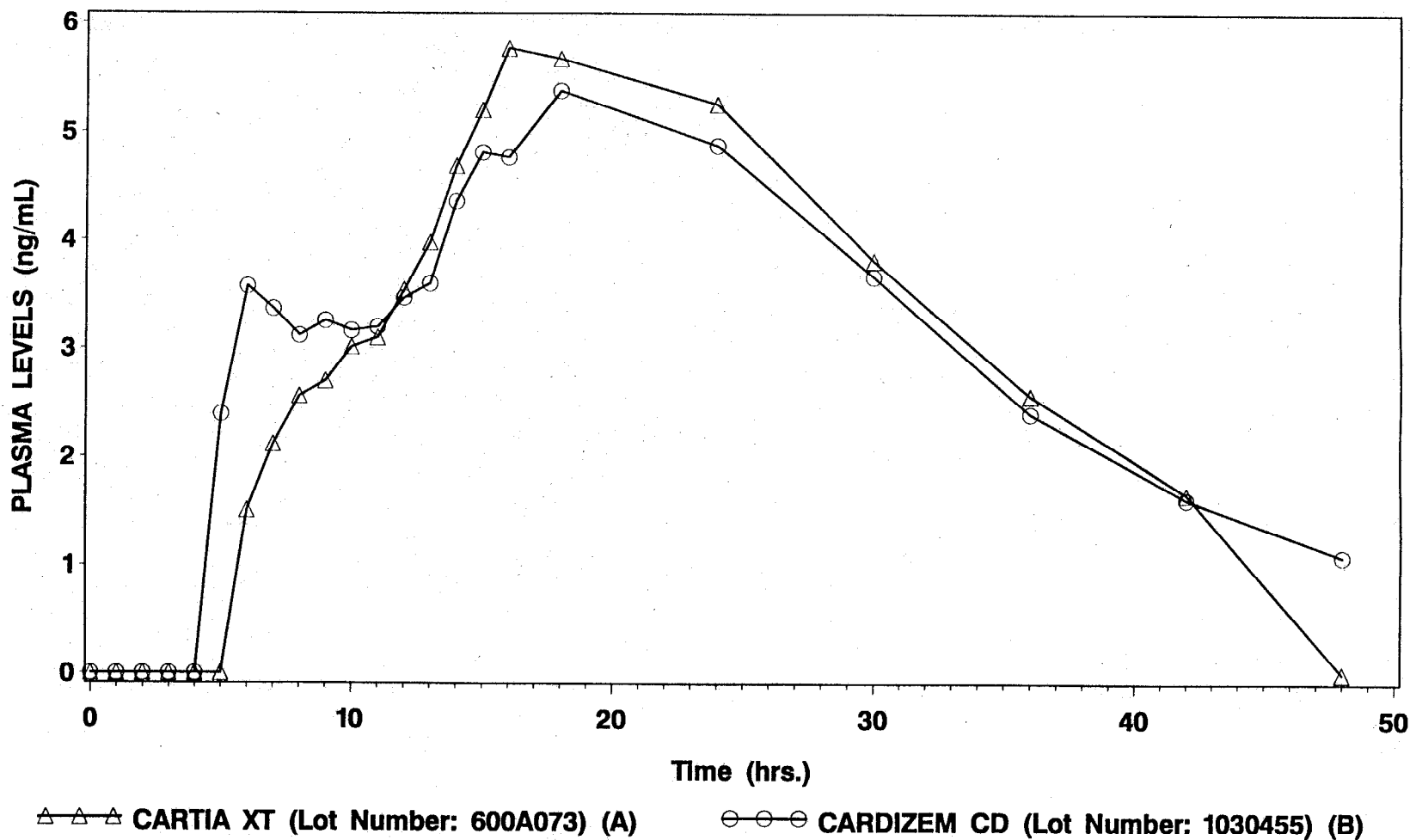


FIGURE 2.26

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 26

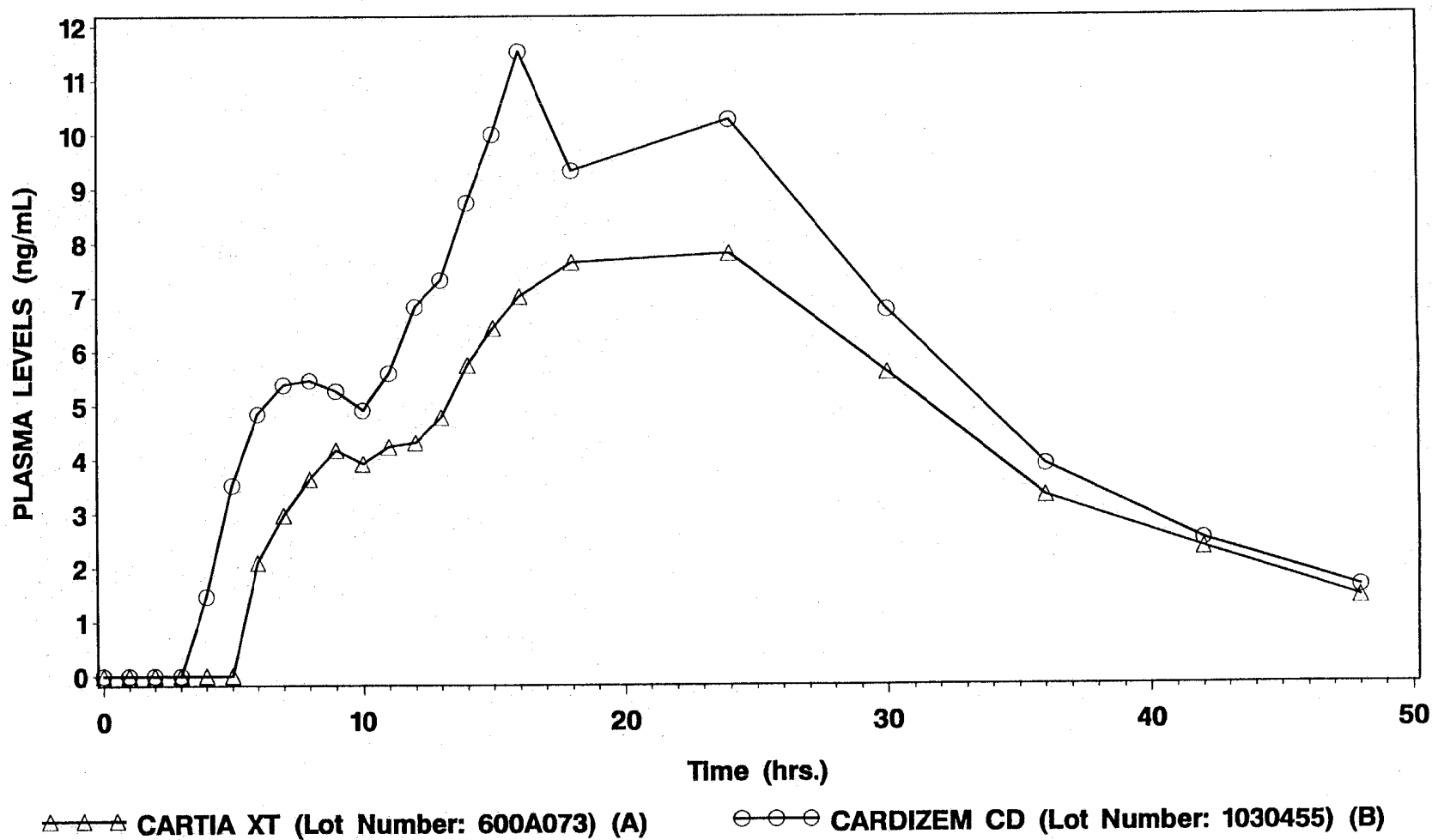


FIGURE 2.27

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 27

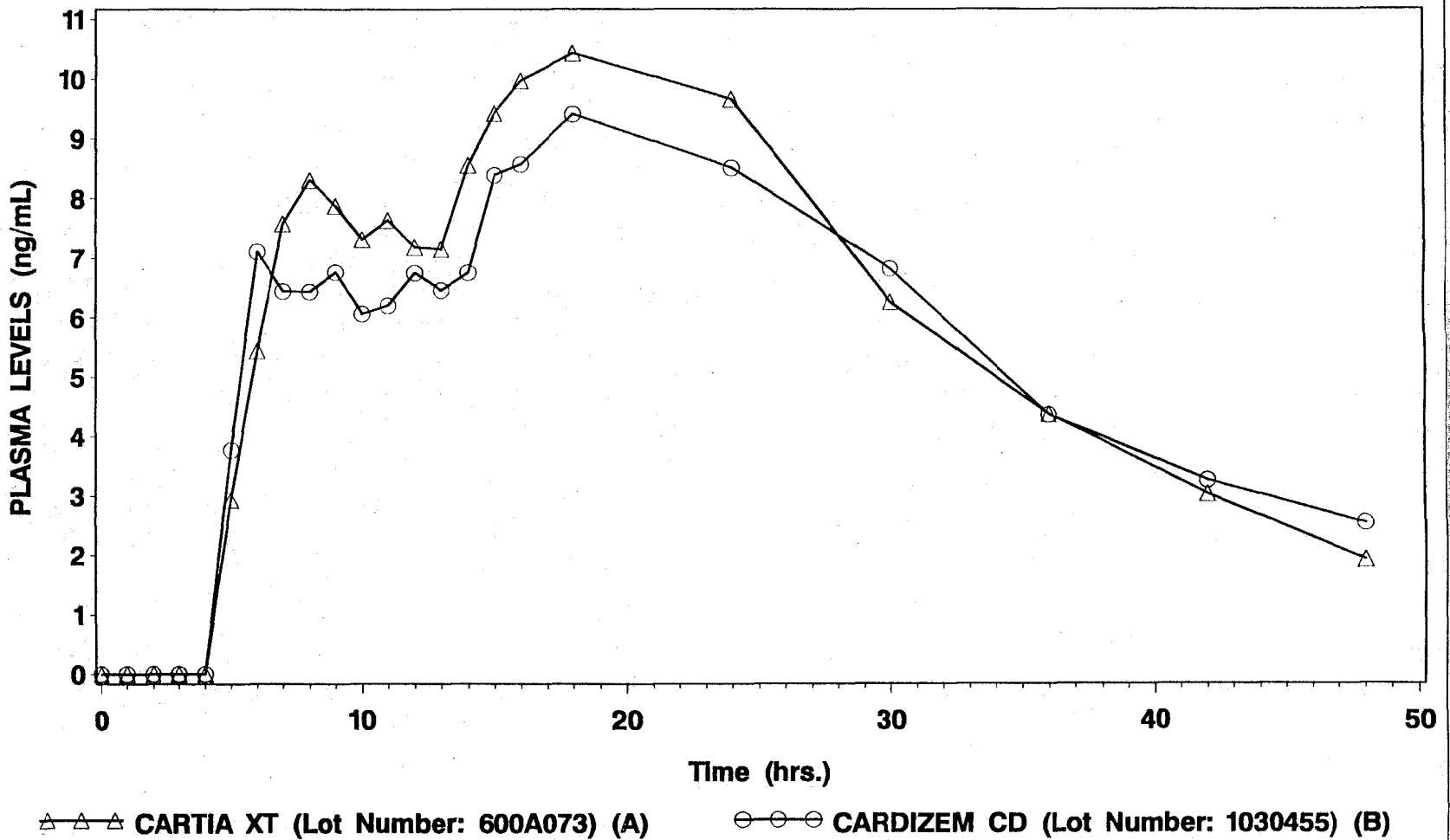


FIGURE 2.28

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 28

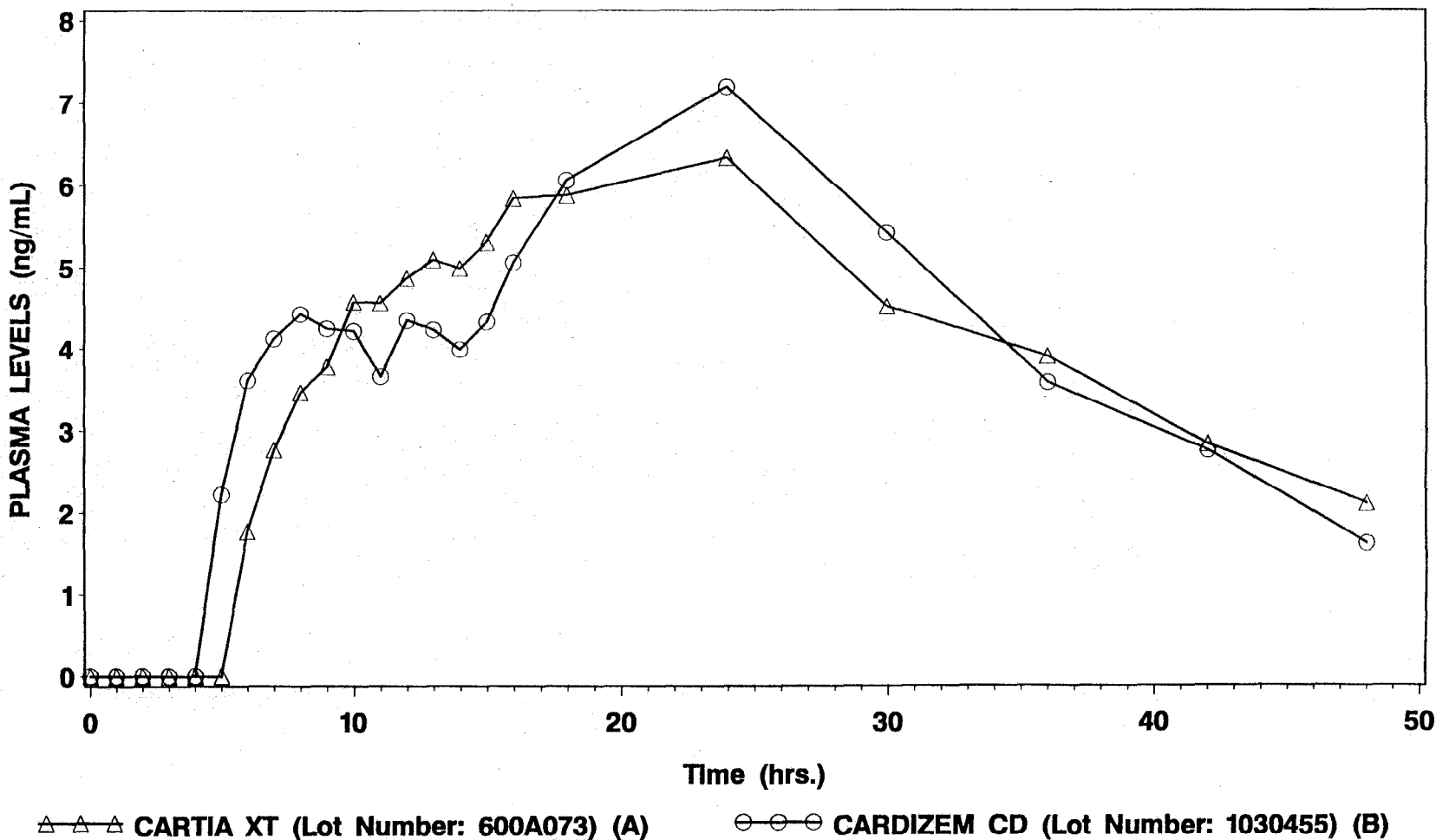


FIGURE 2.29

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=01

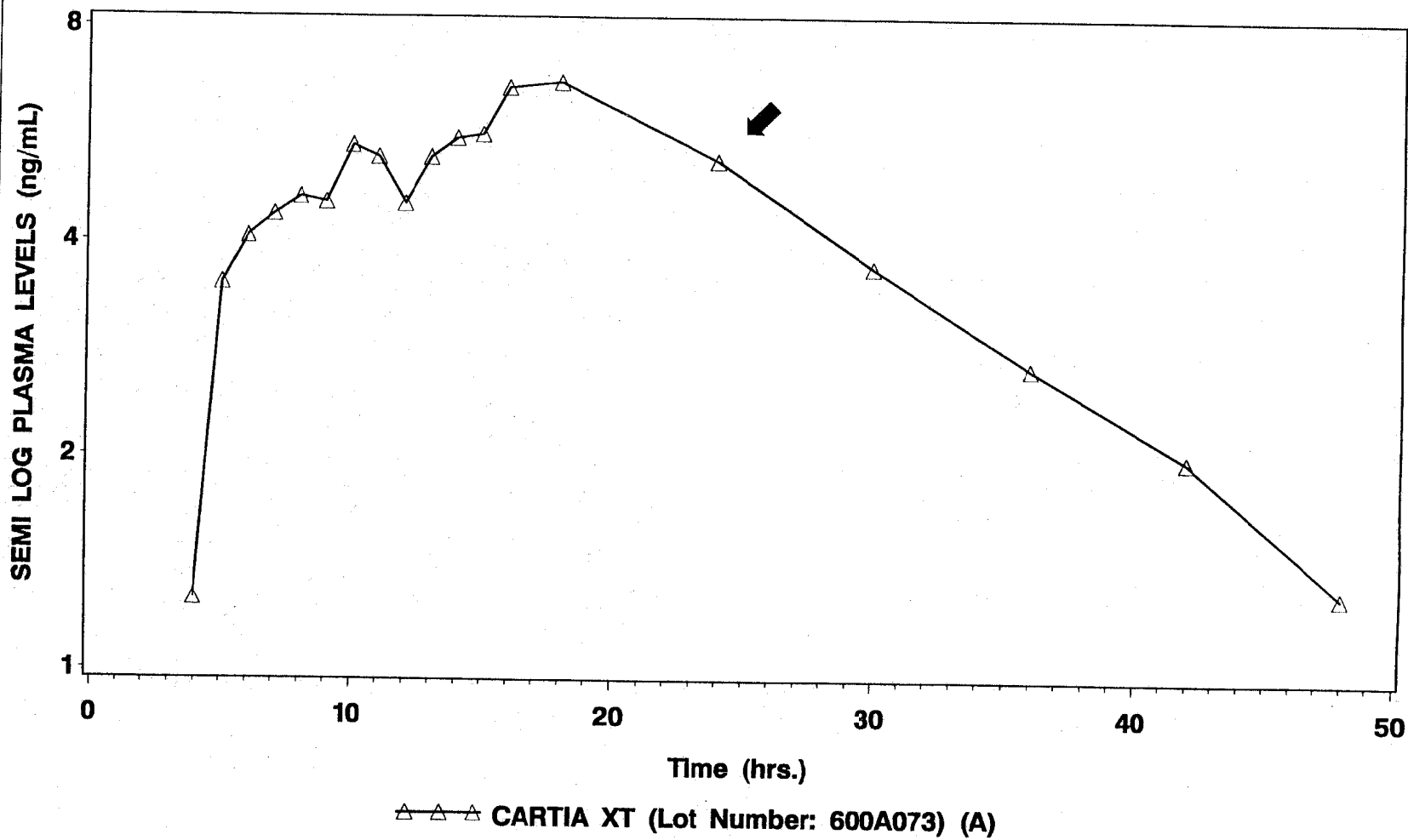


FIGURE 2.30

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 03

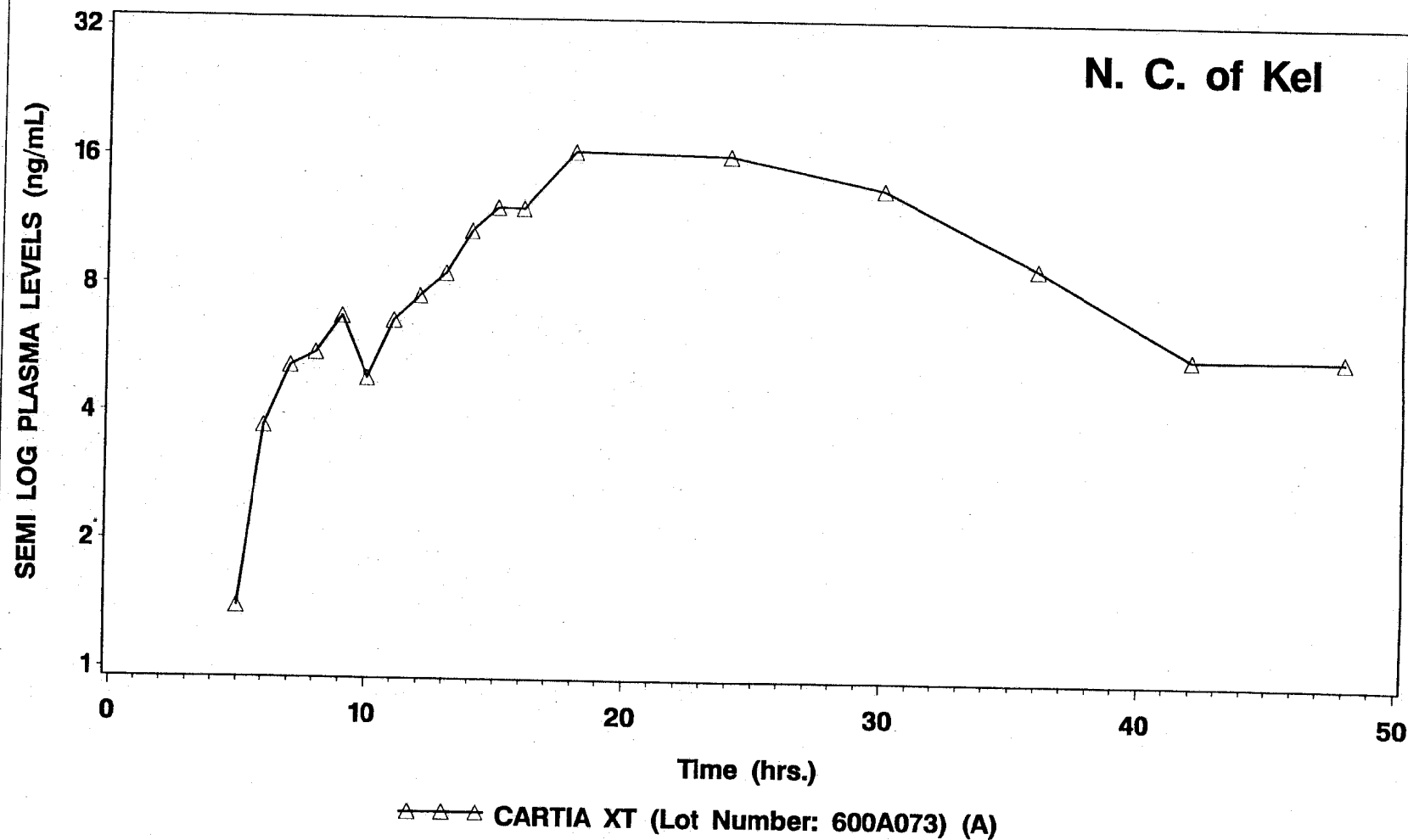


FIGURE 2.31

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 04

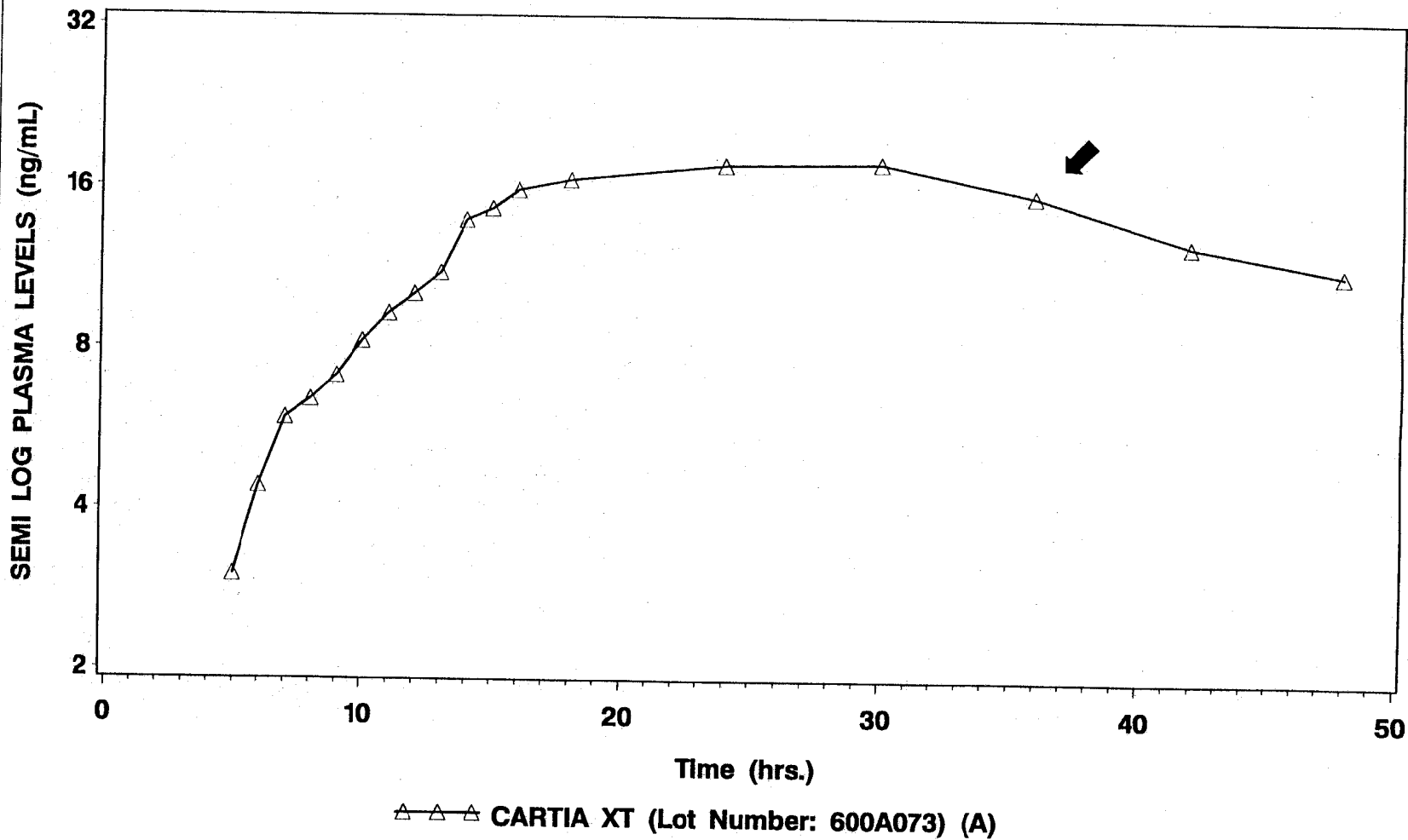
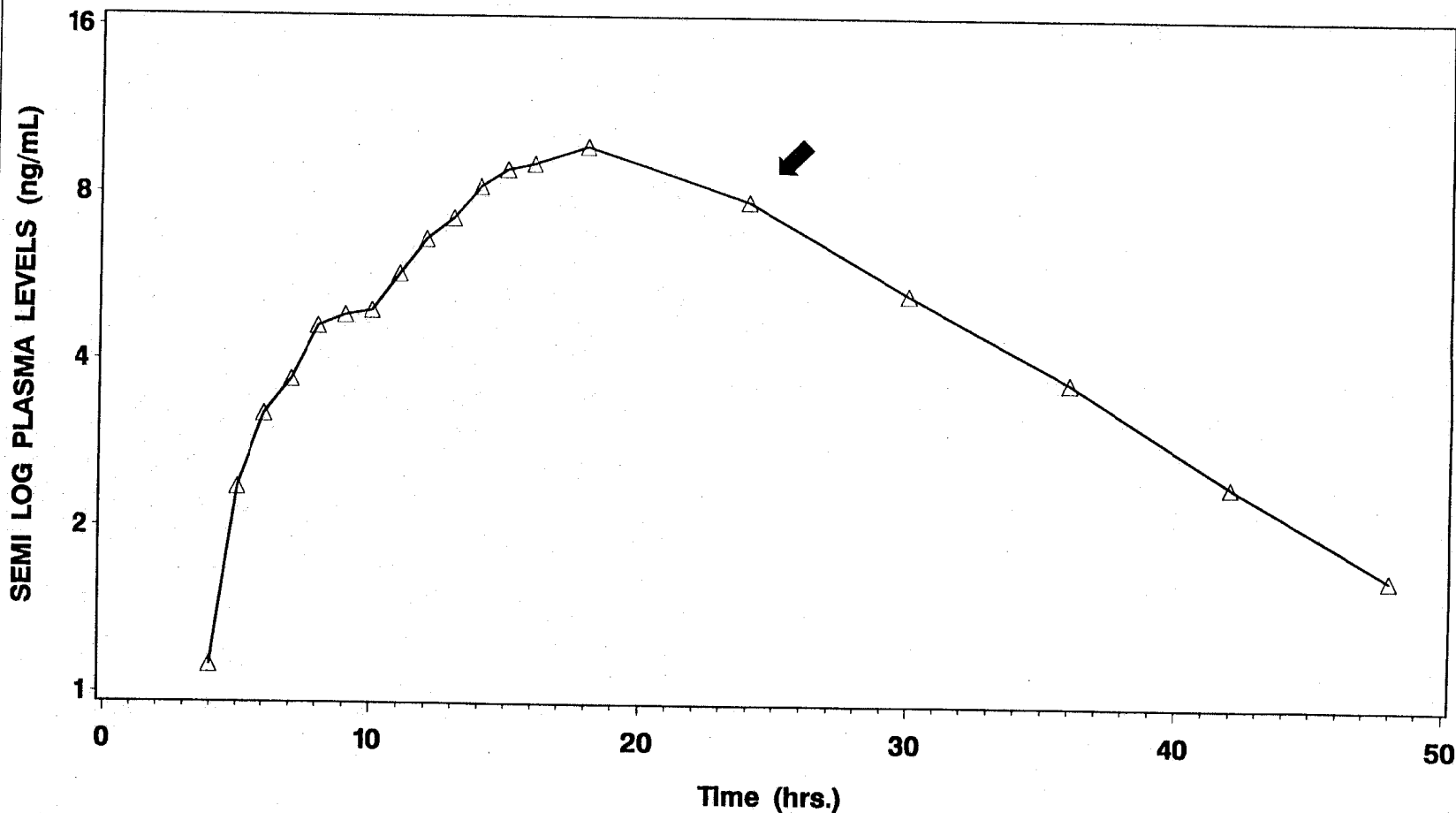


FIGURE 2.32

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 05



△ △ △ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 2.33

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 06

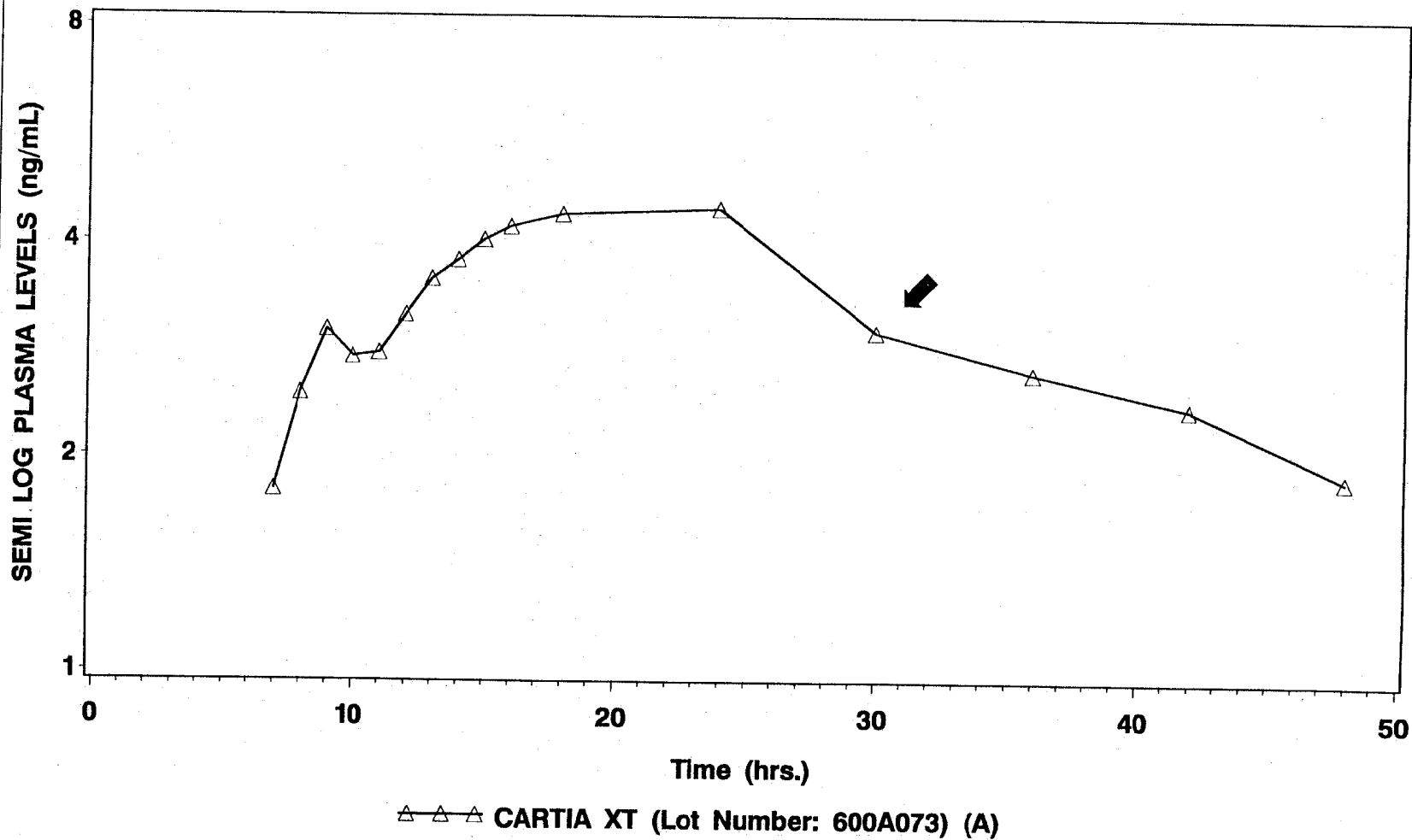


FIGURE 2.34

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 07

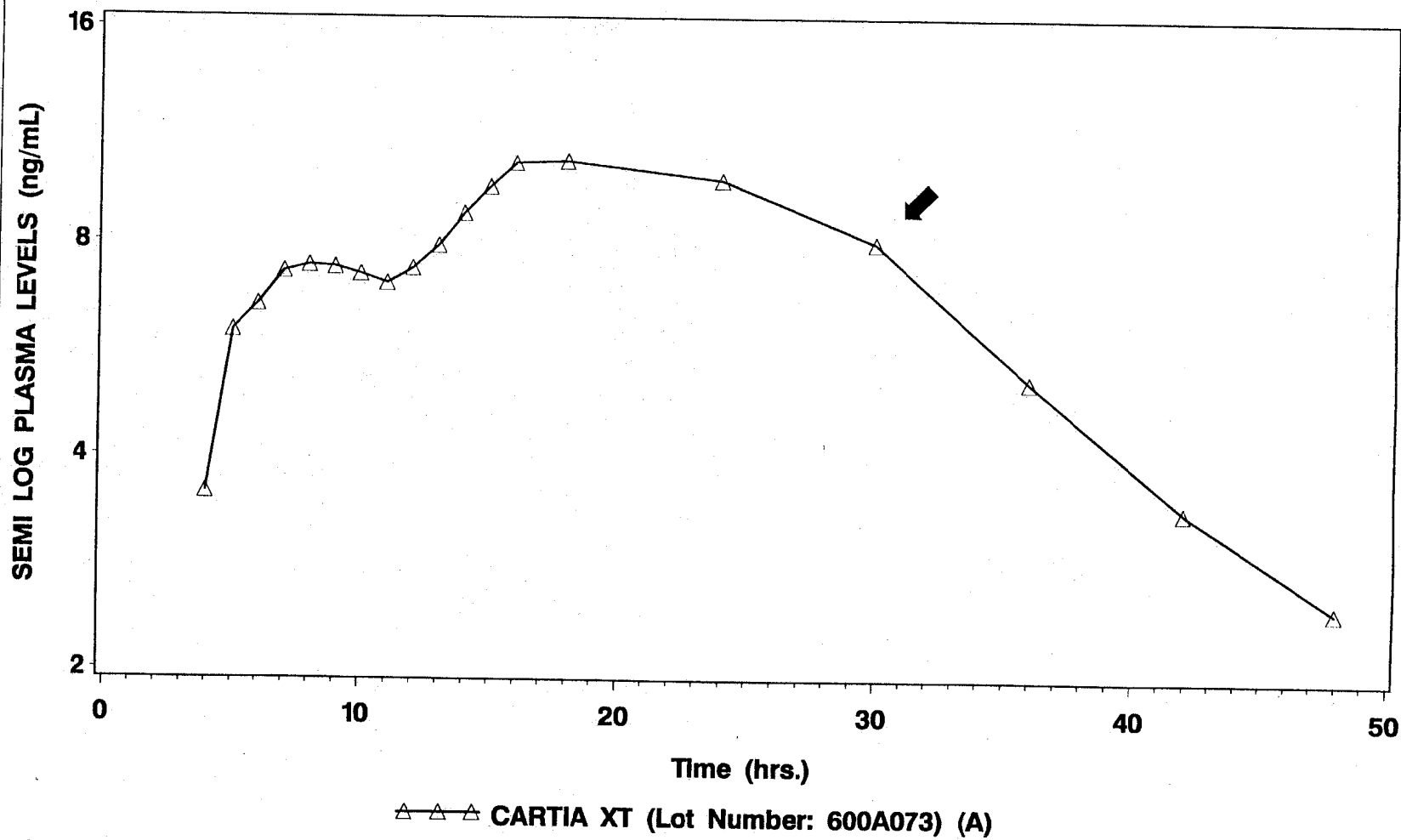


FIGURE 2.35

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 08

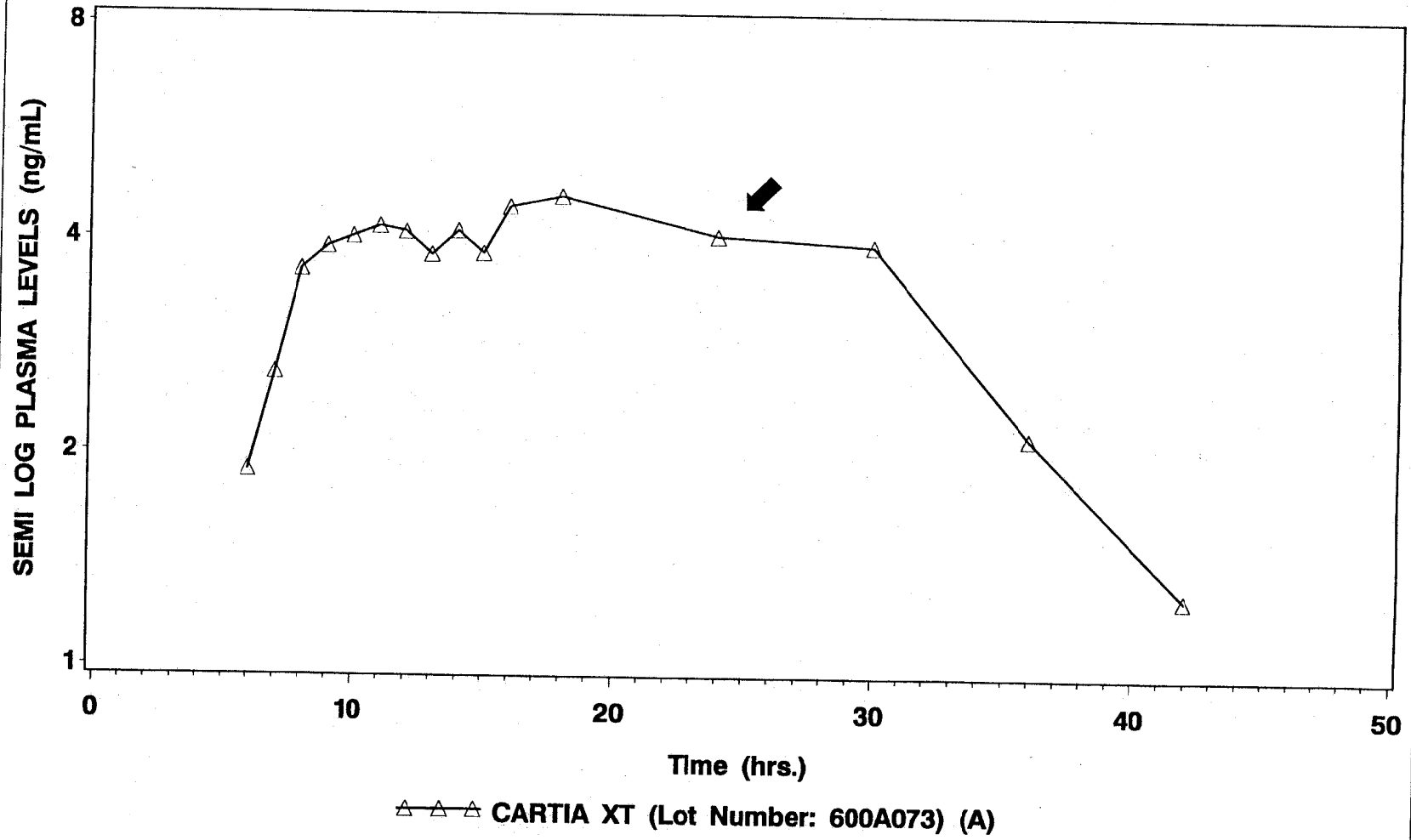


FIGURE 2.36

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 09

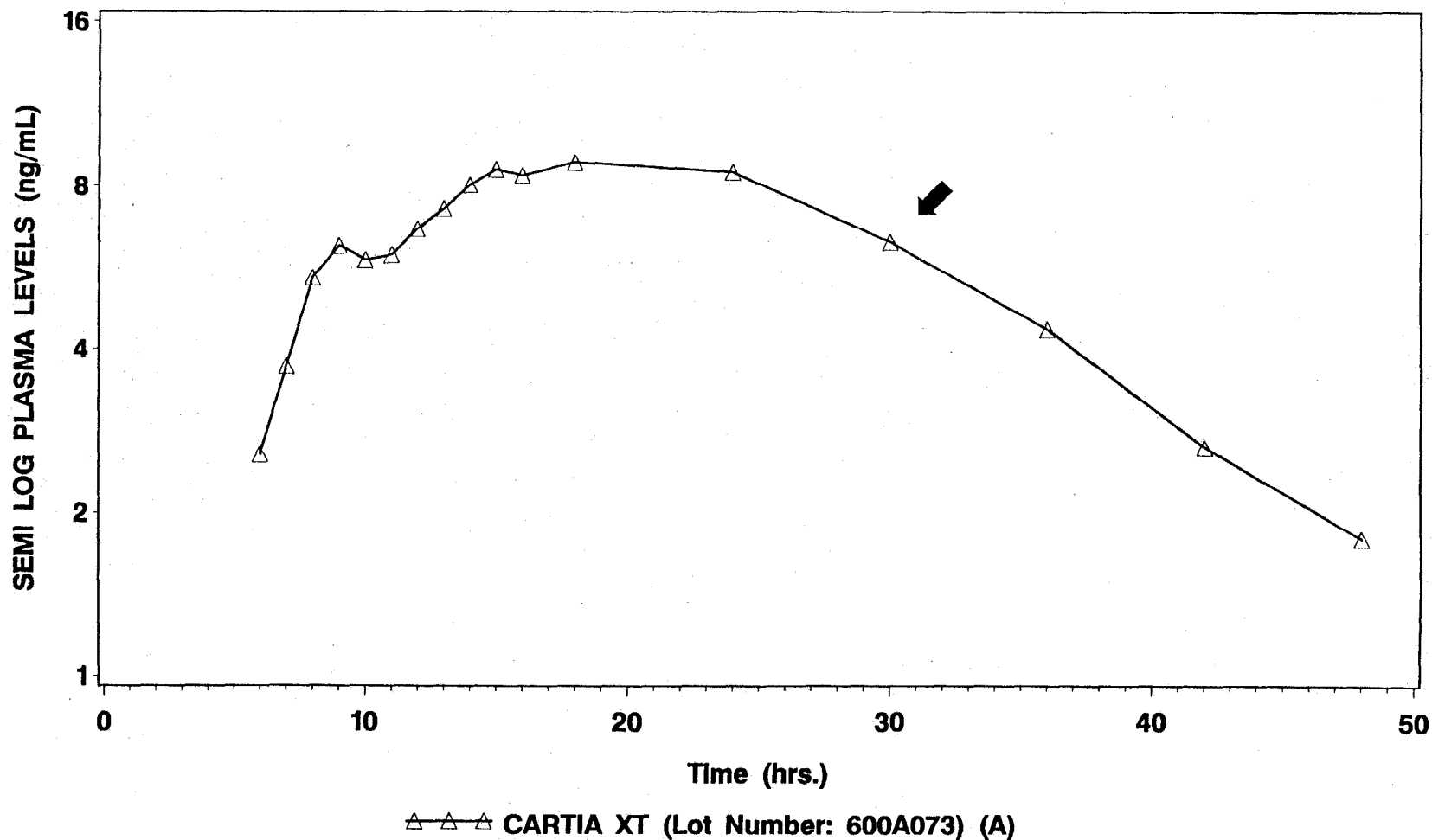
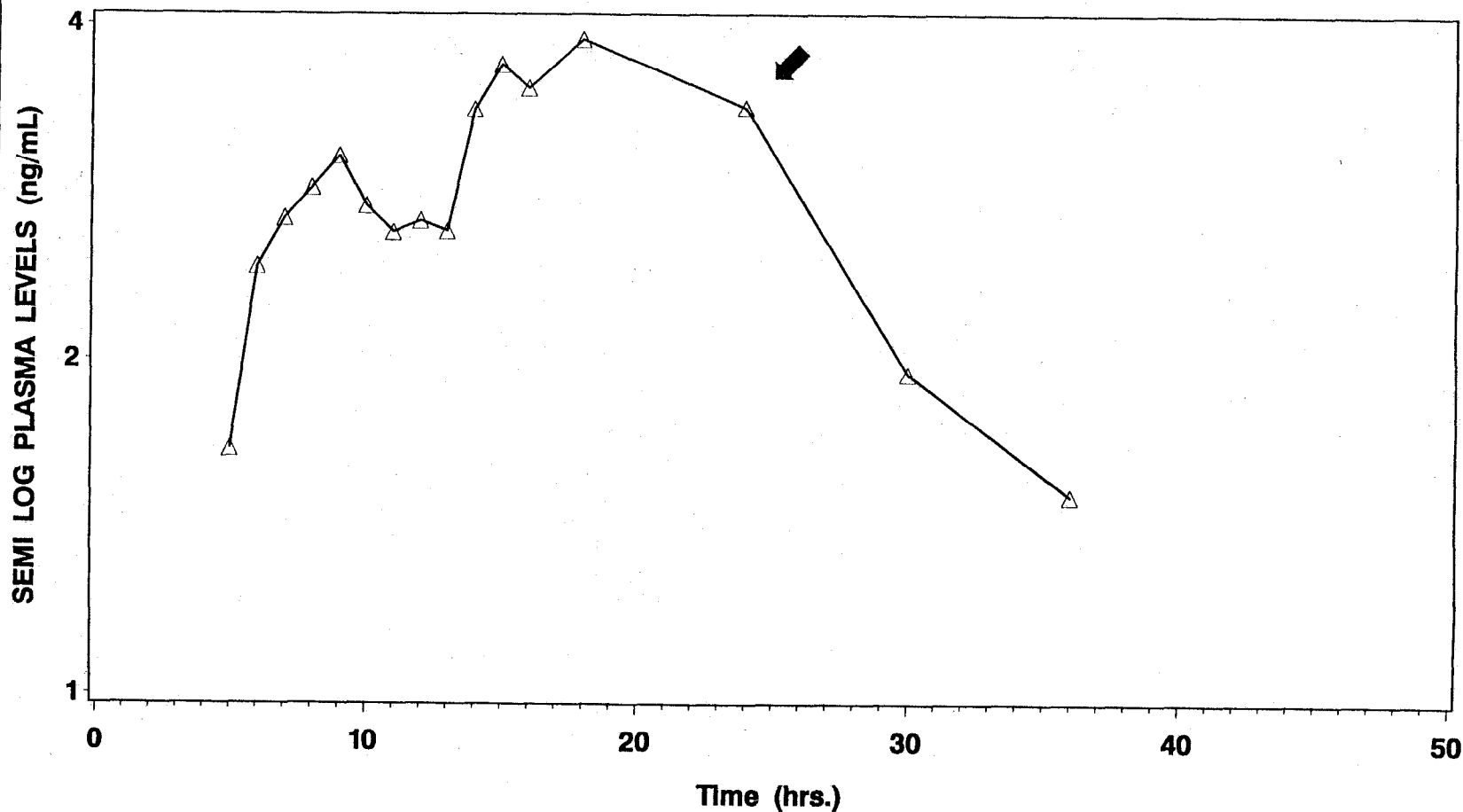


FIGURE 2.37

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 10



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 2.38

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 11

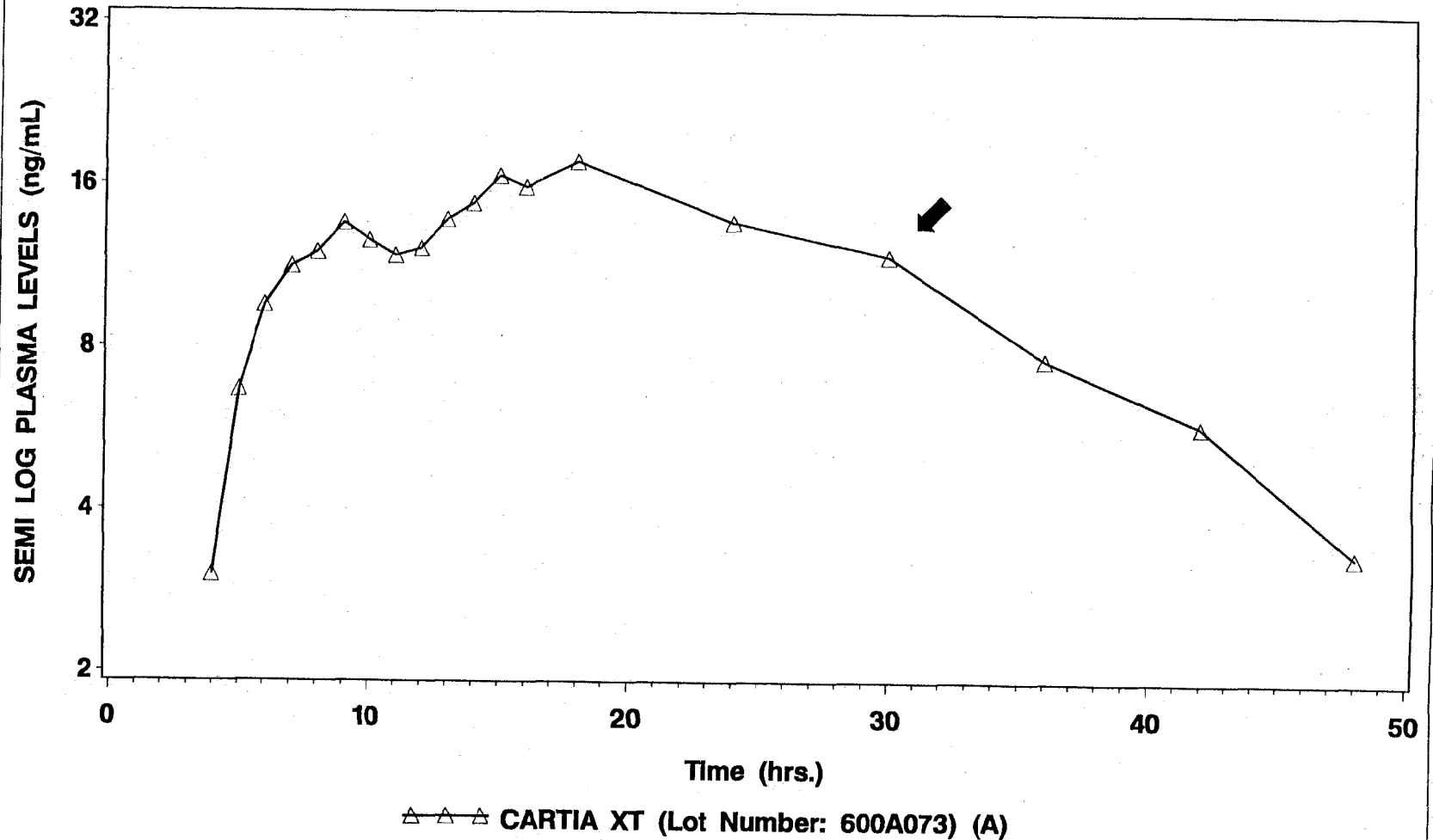
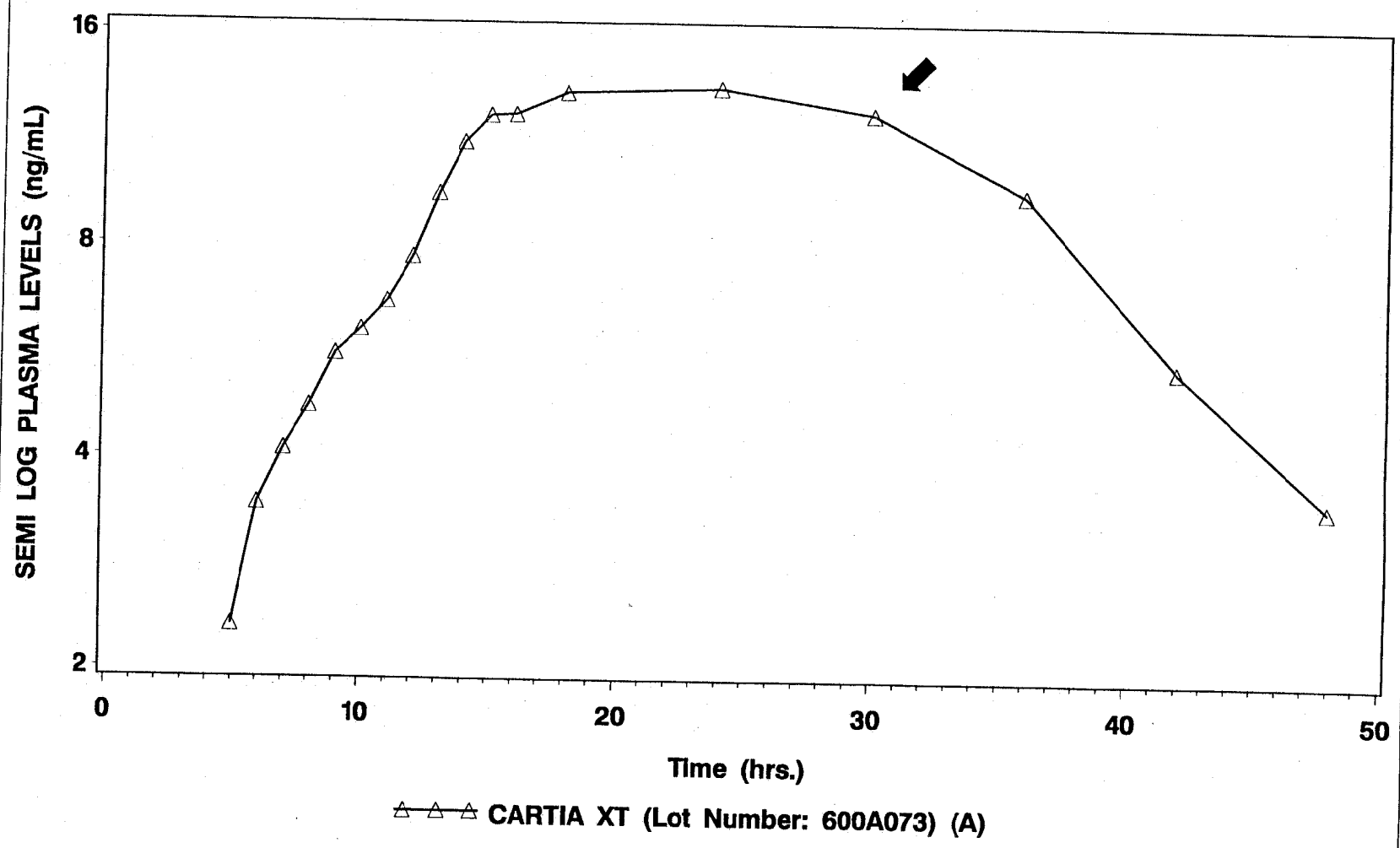


FIGURE 2.39

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 12

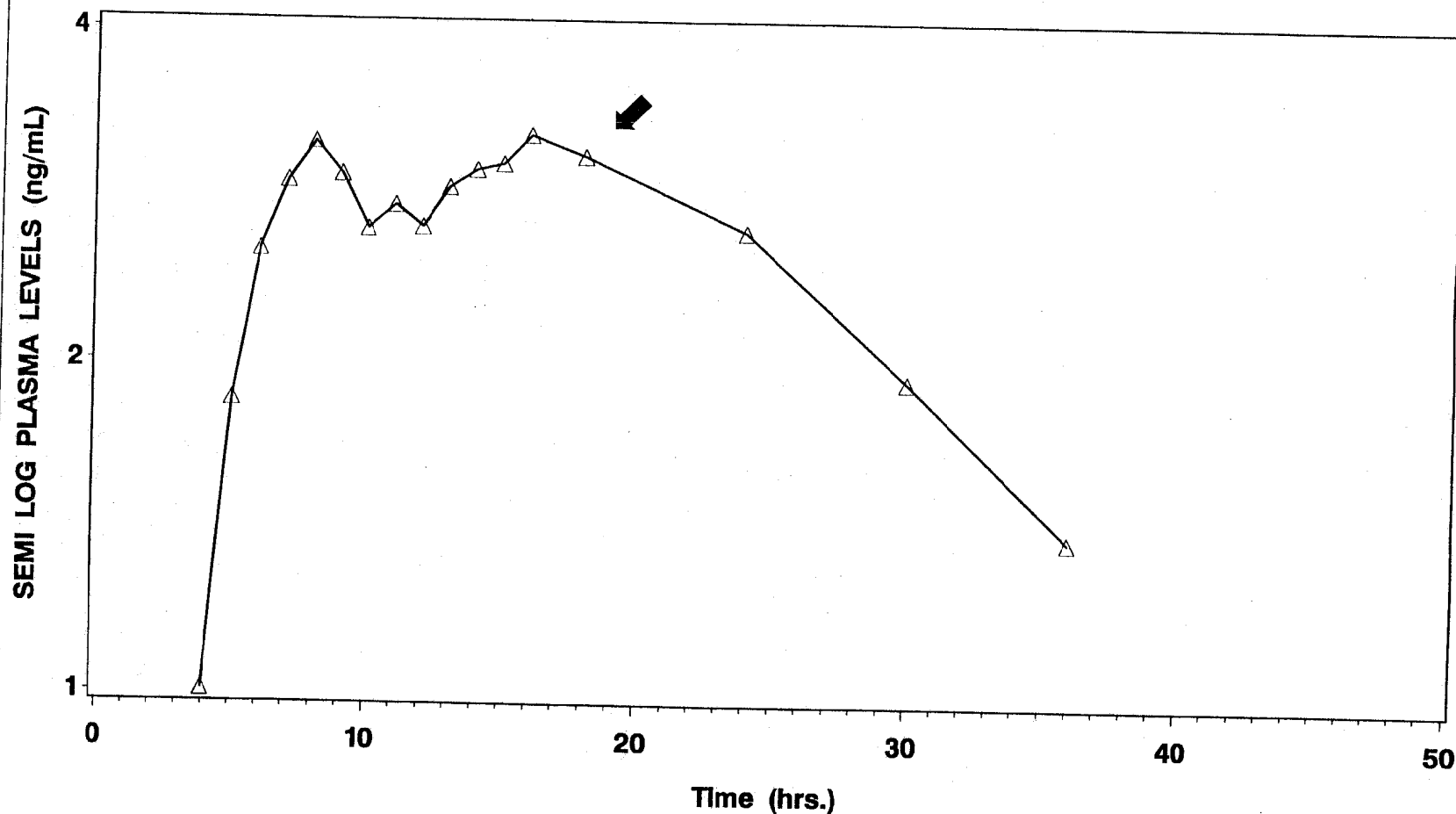


△△△ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 2.40

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=13



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 2.41

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 14

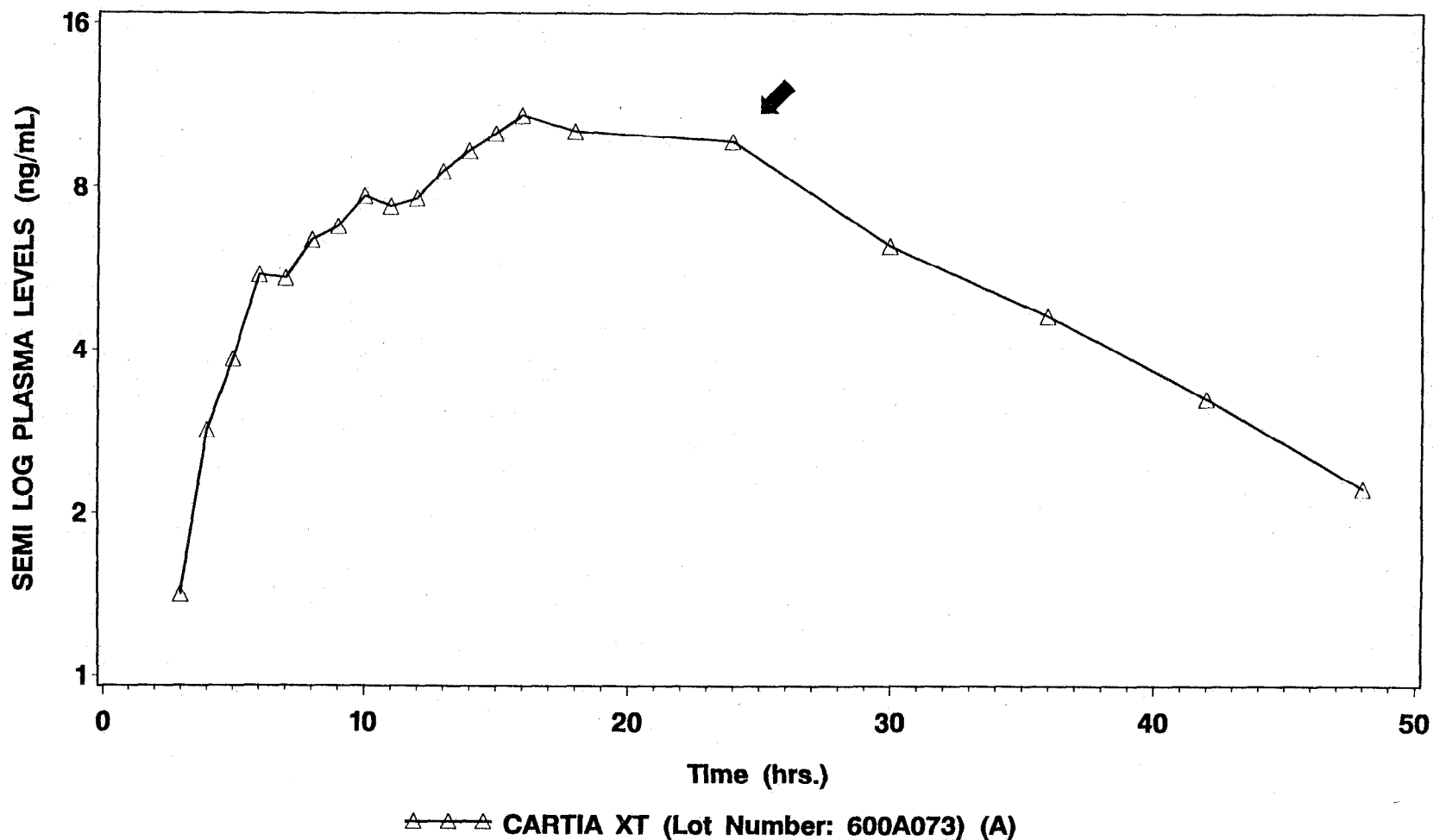


FIGURE 2.42

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 15

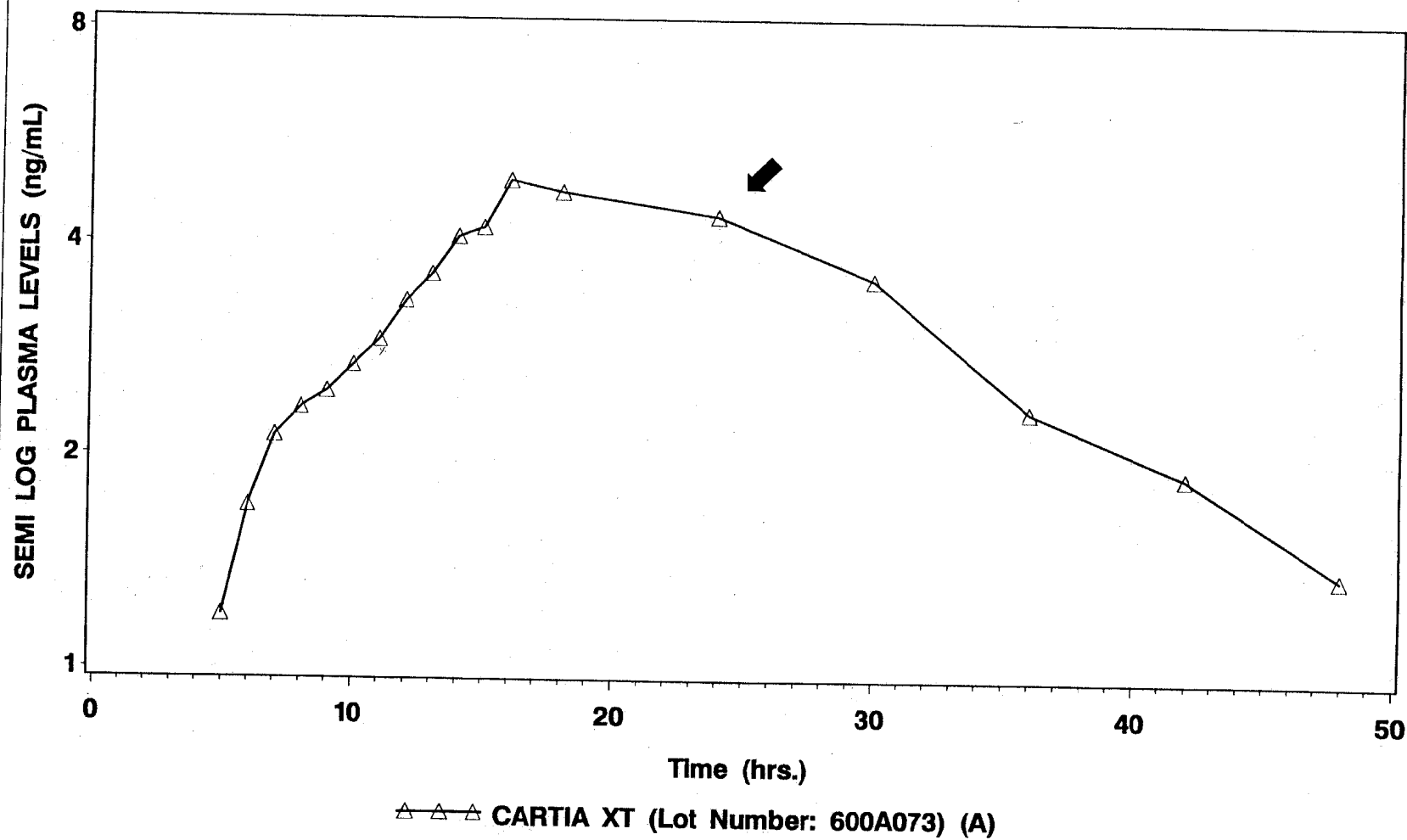
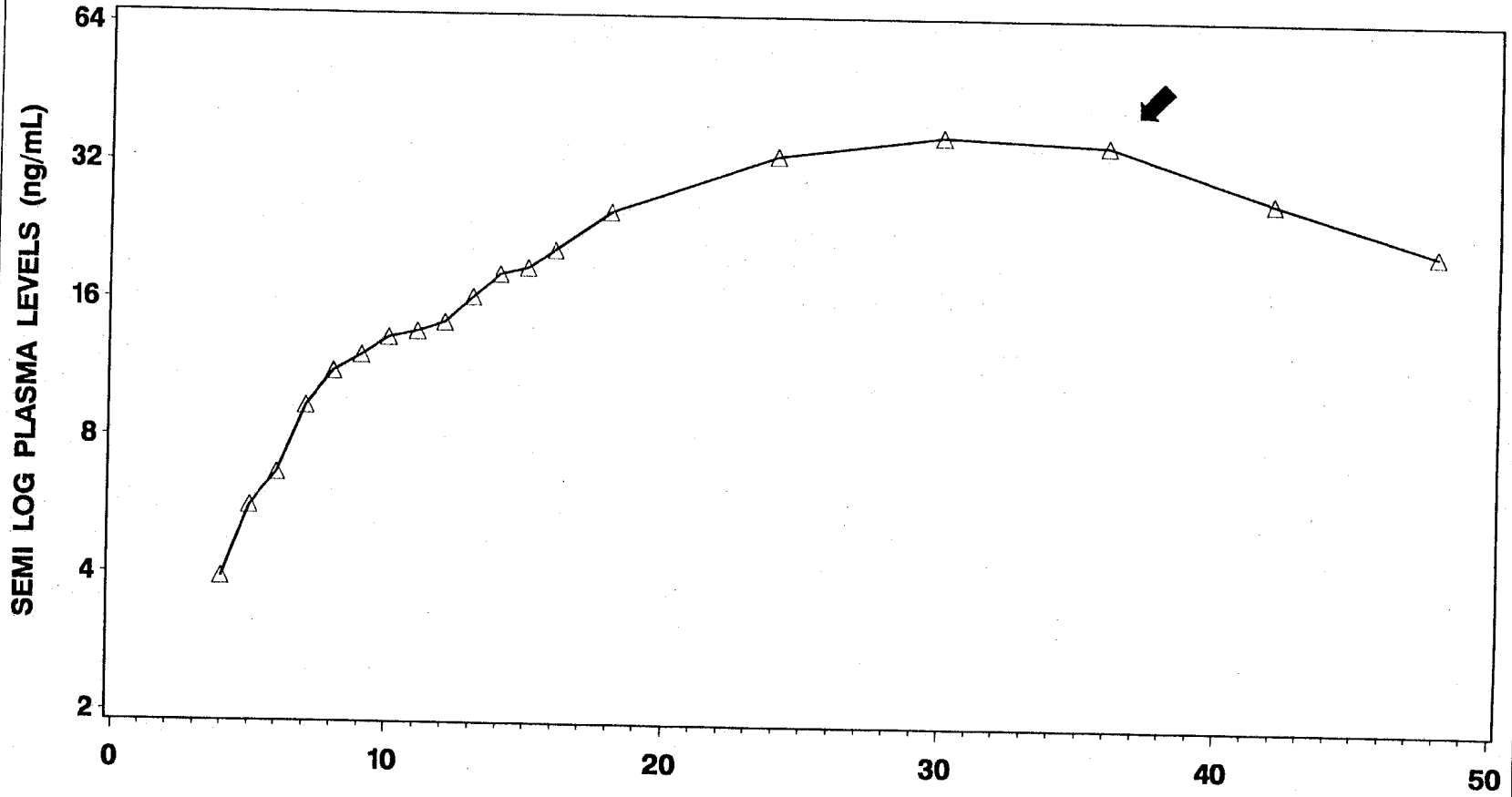


FIGURE 2.43

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=16

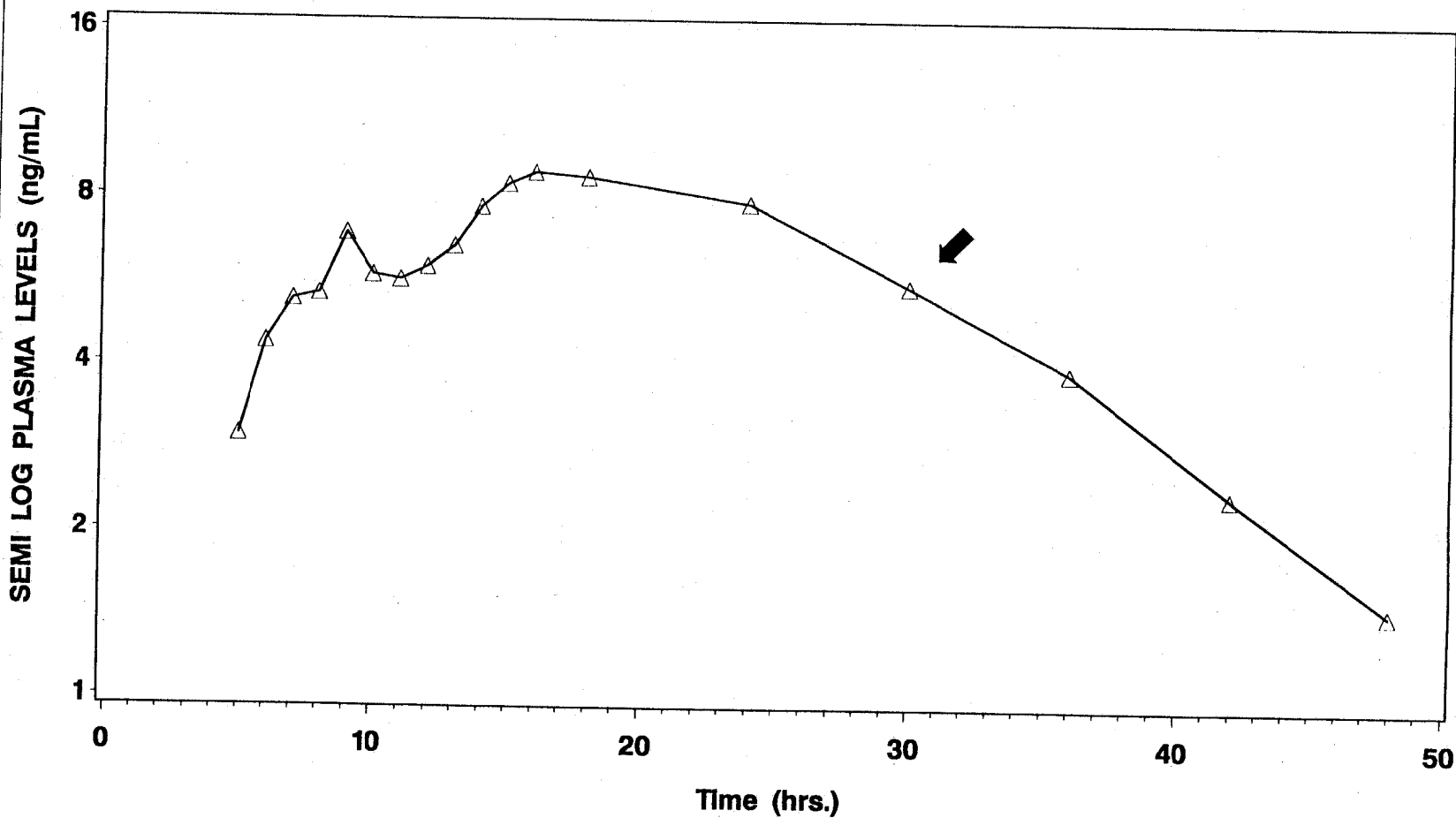


△-△-△ **CARTIA XT (Lot Number: 600A073) (A)**

FIGURE 2.44

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=17



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 2.45

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=18

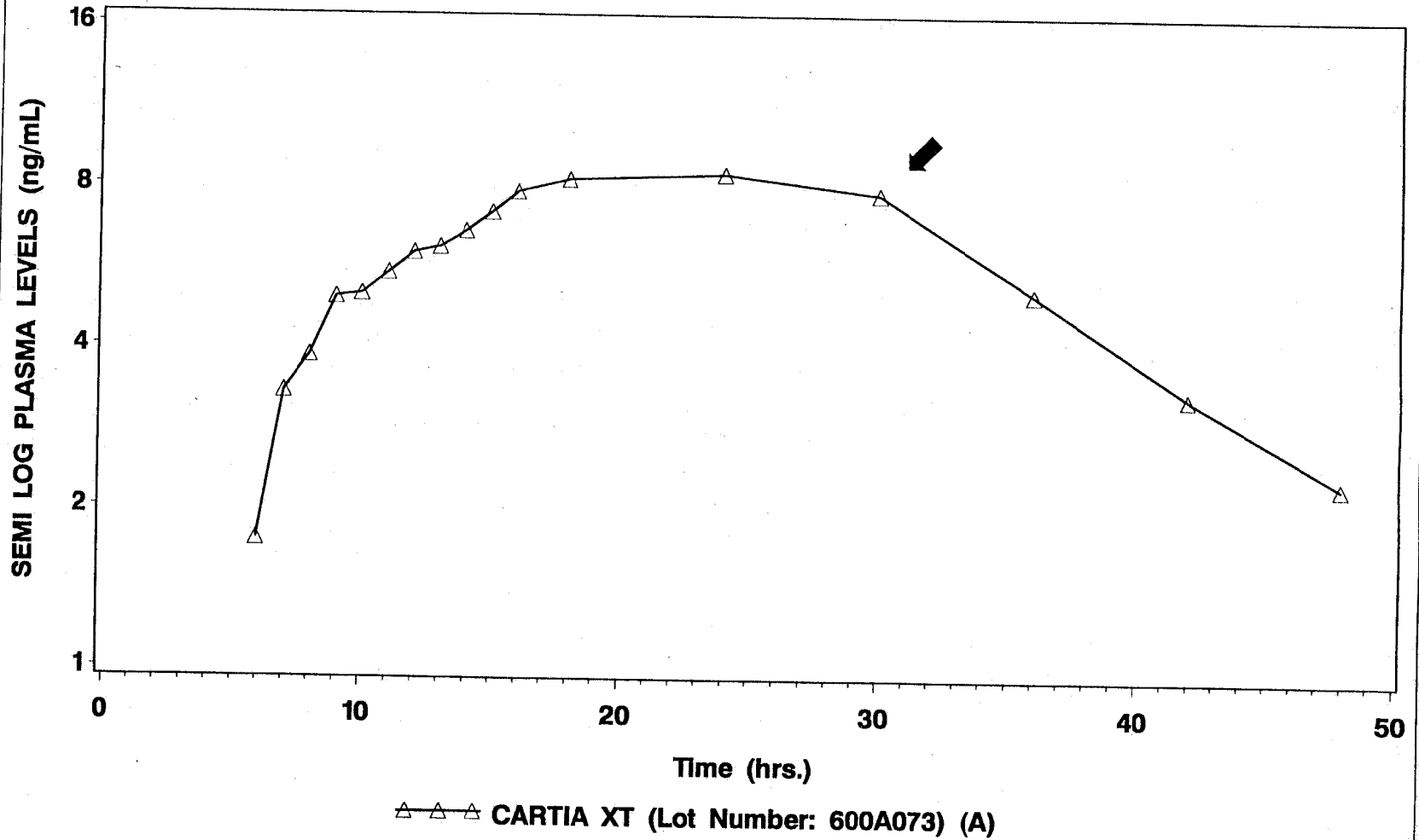


FIGURE 2.46

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 19

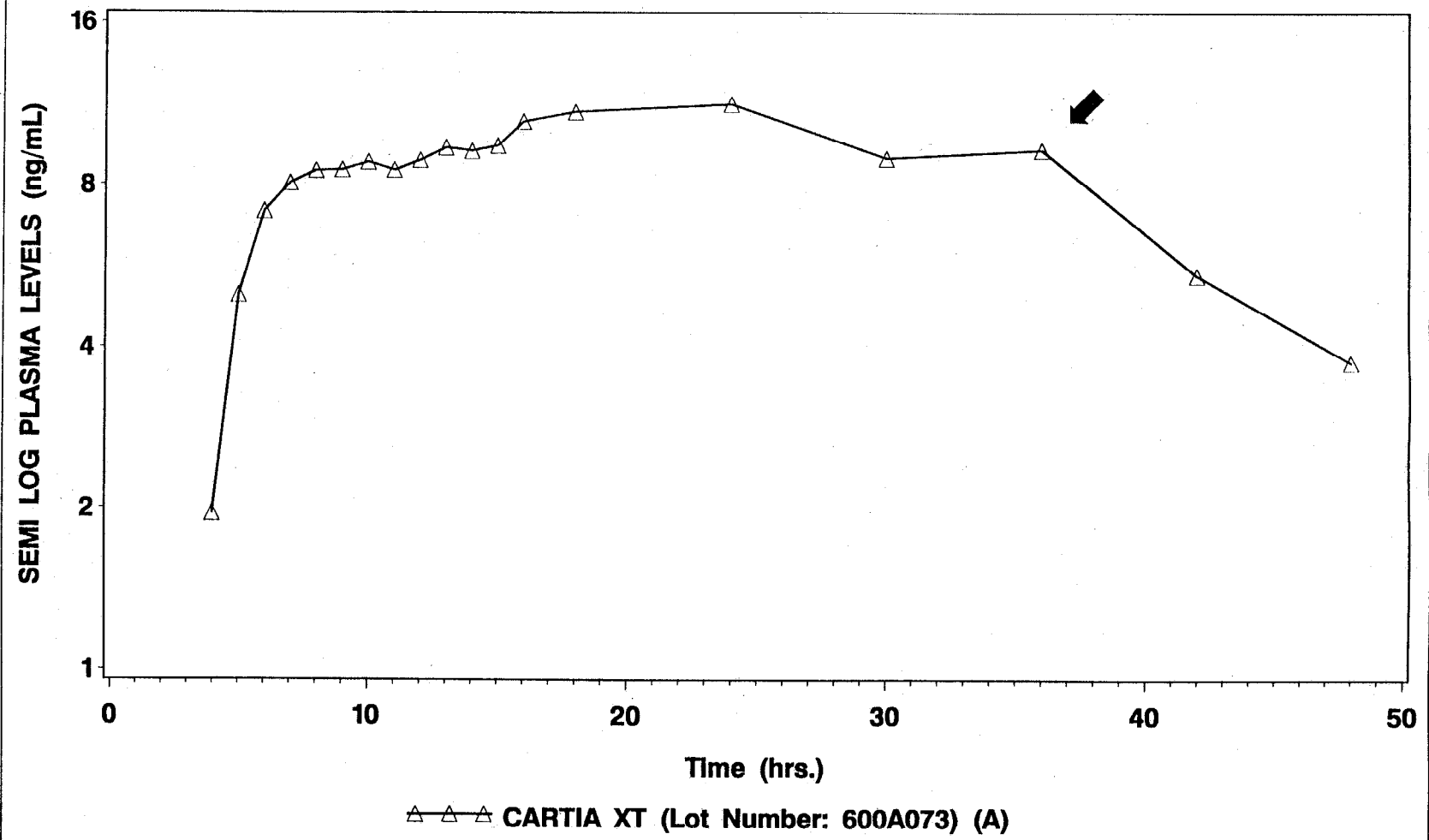


FIGURE 2.47

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 20

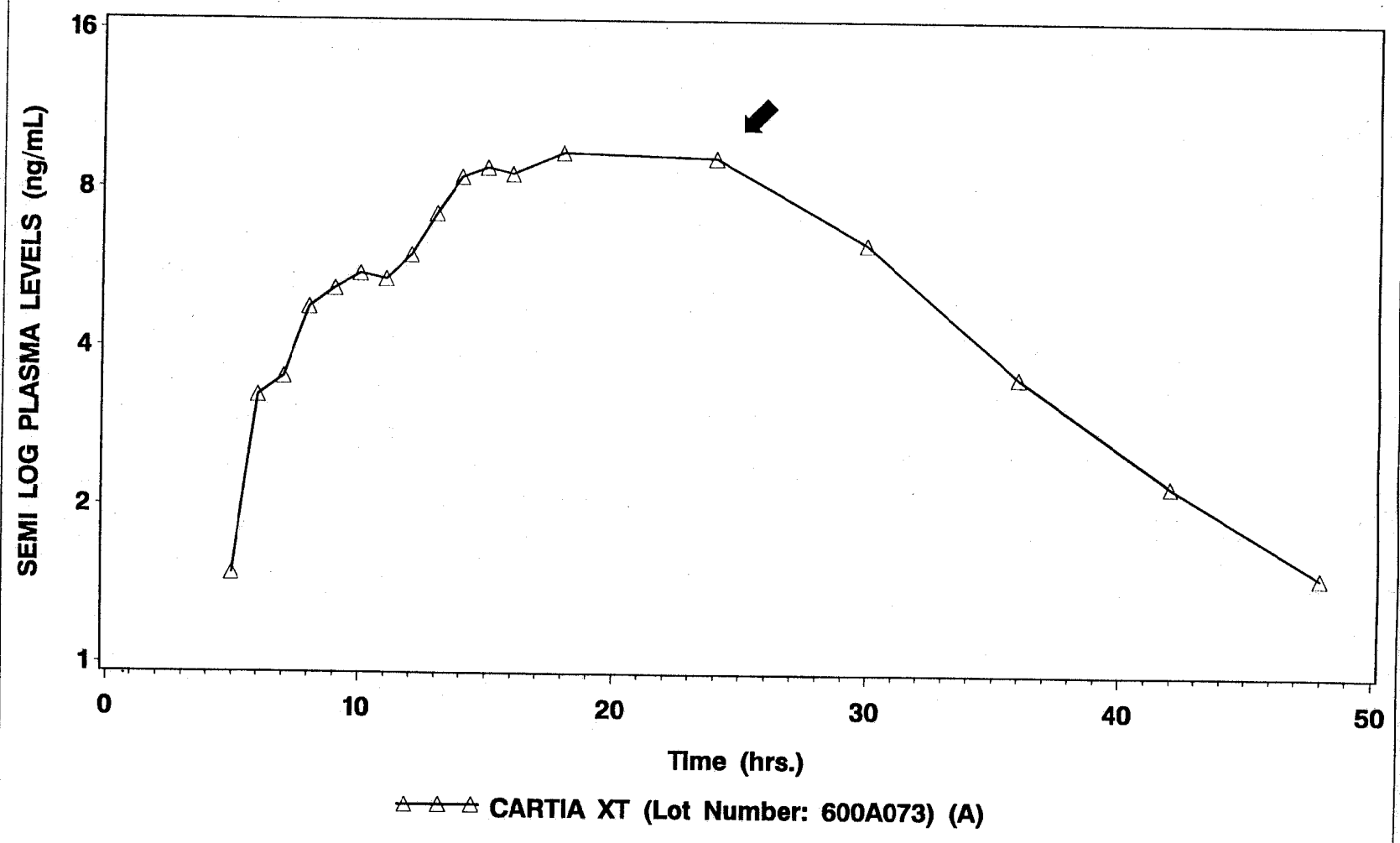


FIGURE 2.48

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 21

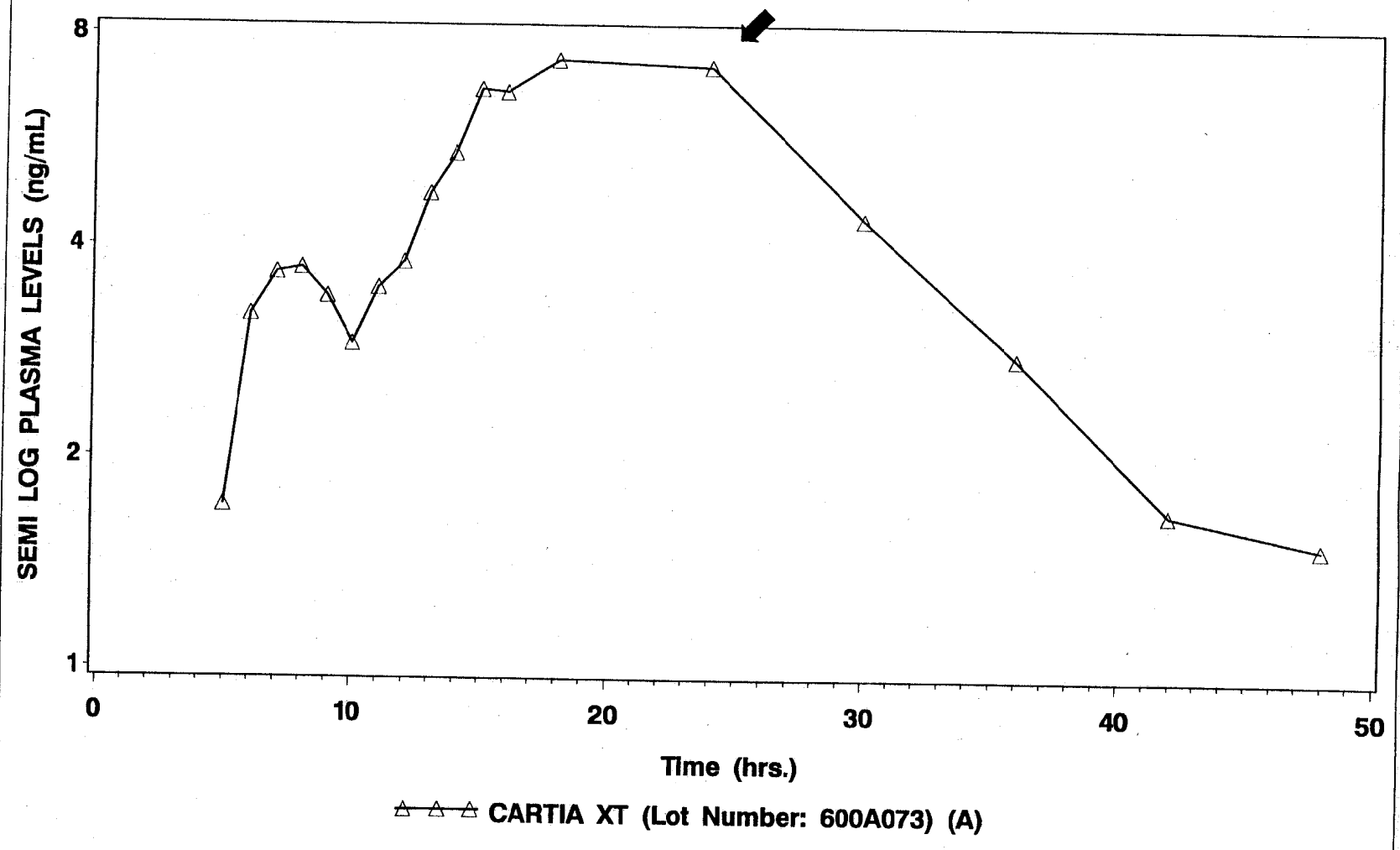


FIGURE 2.49

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 22

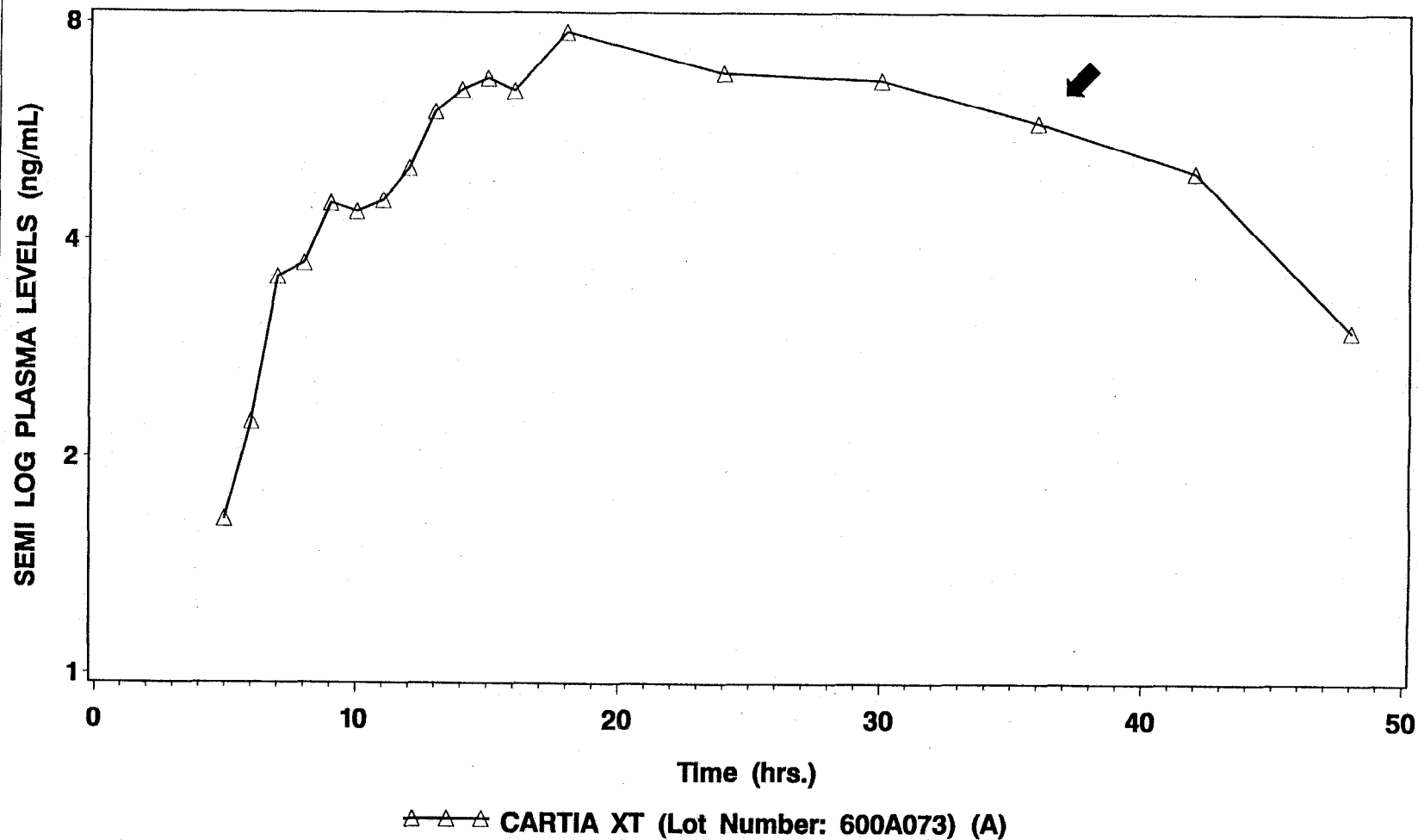


FIGURE 2.50

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 23

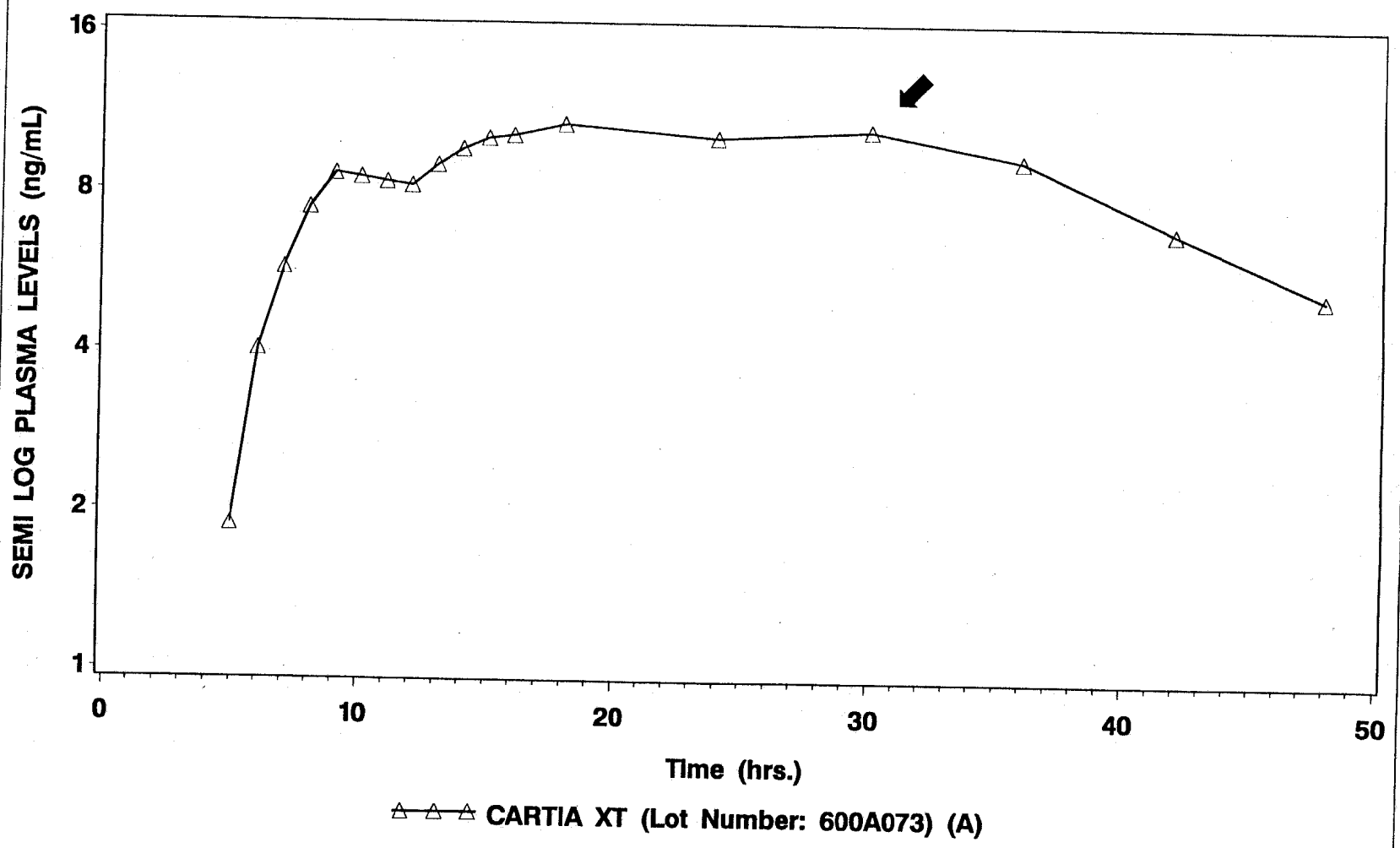


FIGURE 2.51

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 24

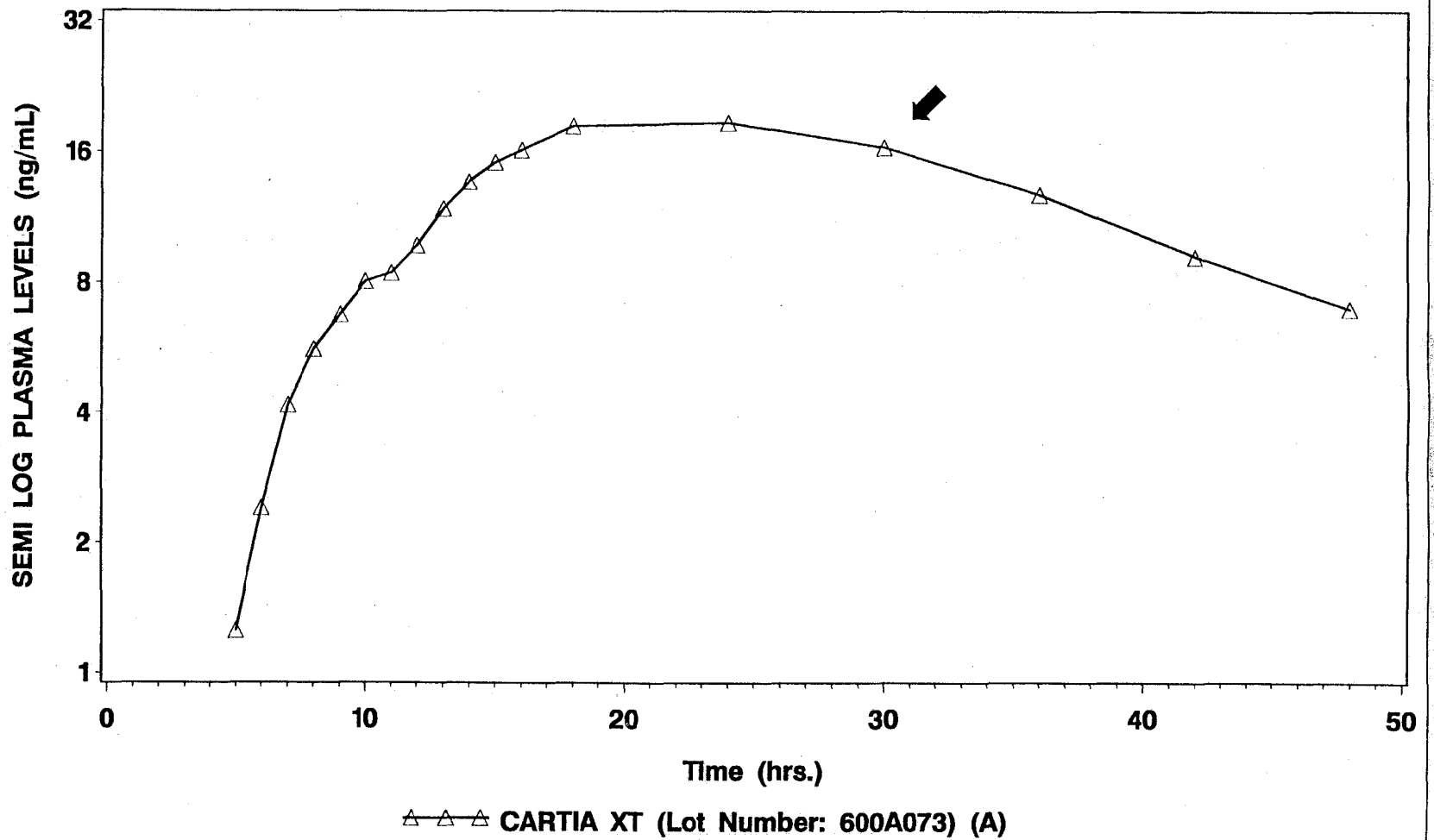


FIGURE 2.52

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 25

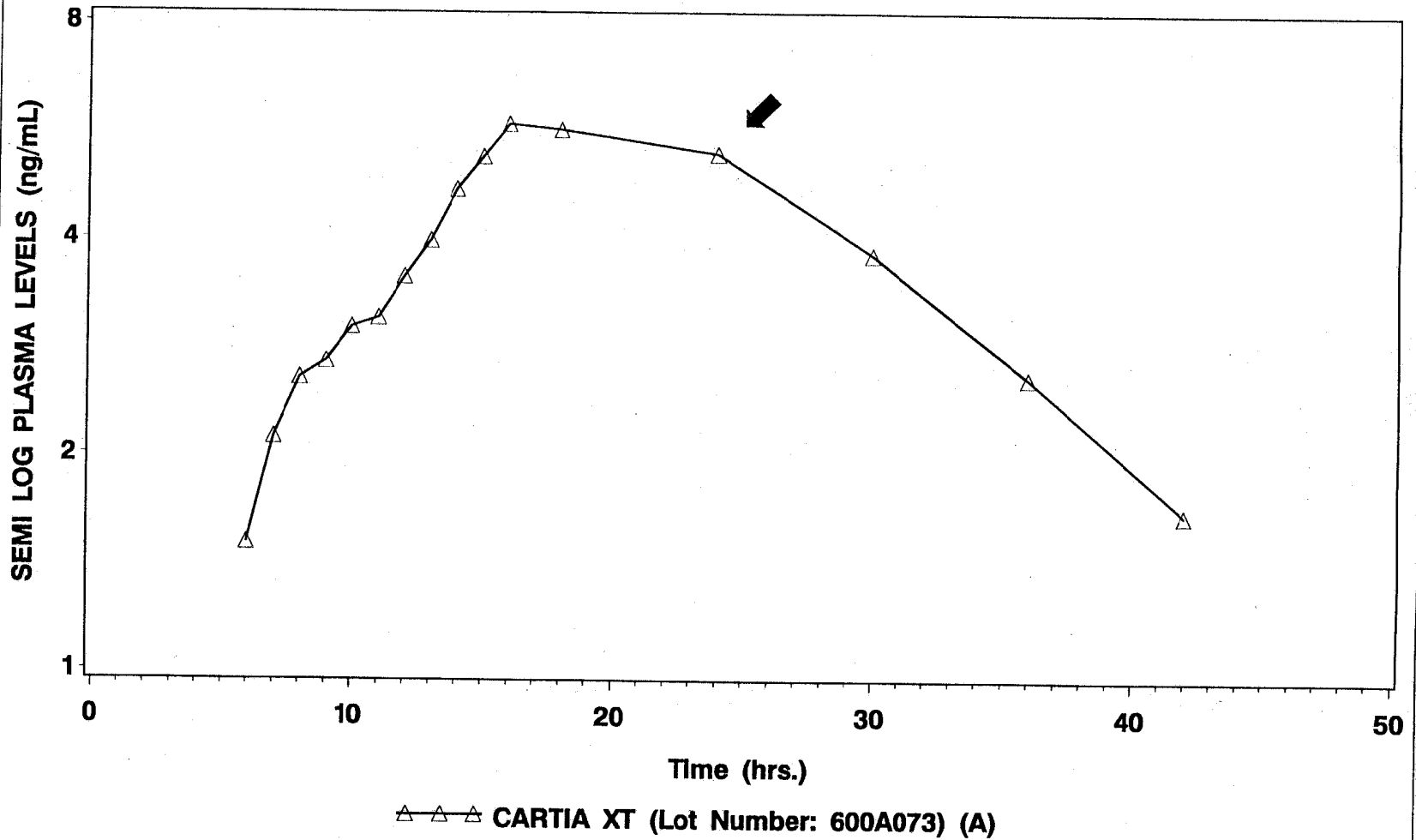


FIGURE 2.53

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 26

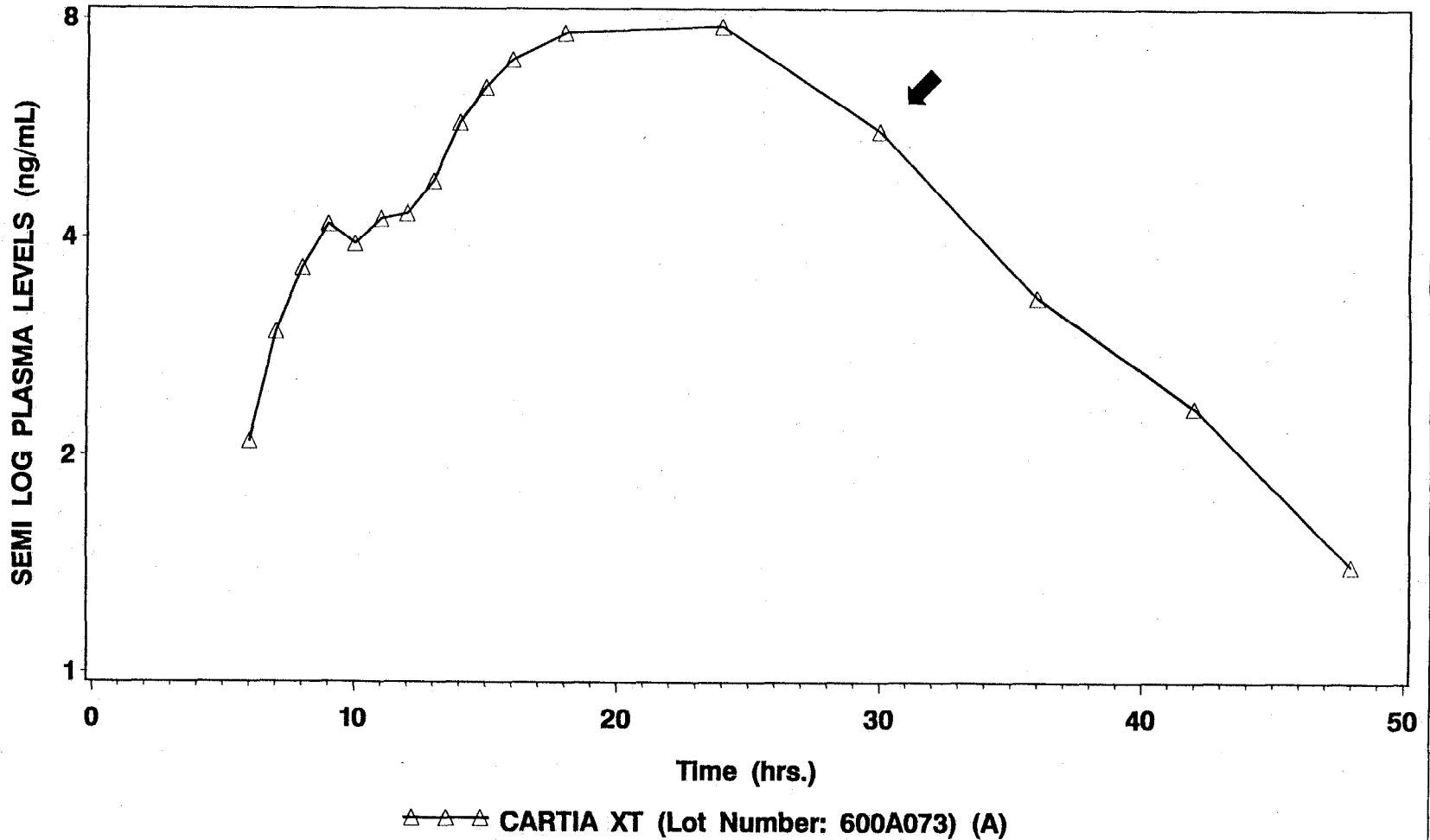


FIGURE 2.54

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 27

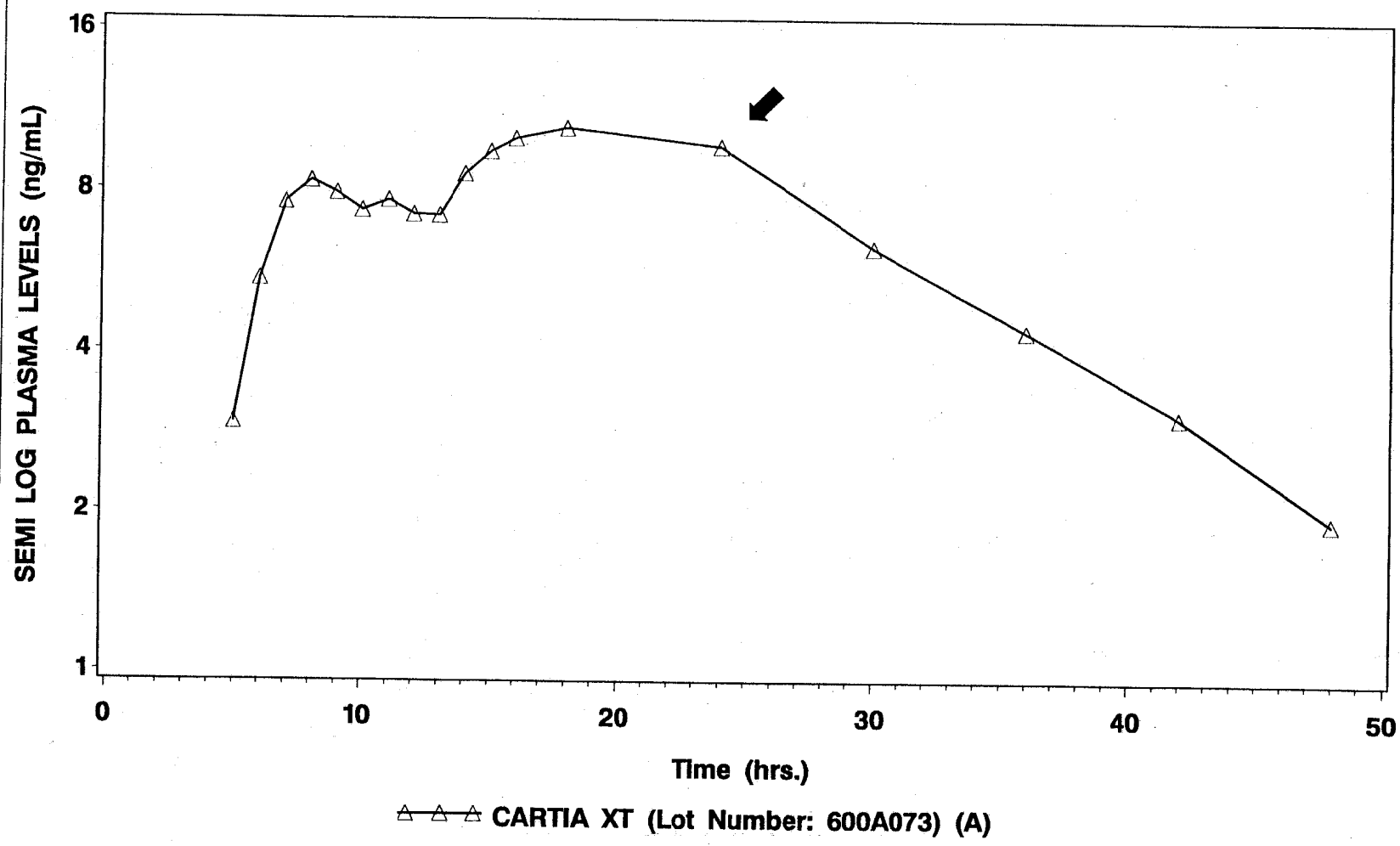


FIGURE 2.55

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 28

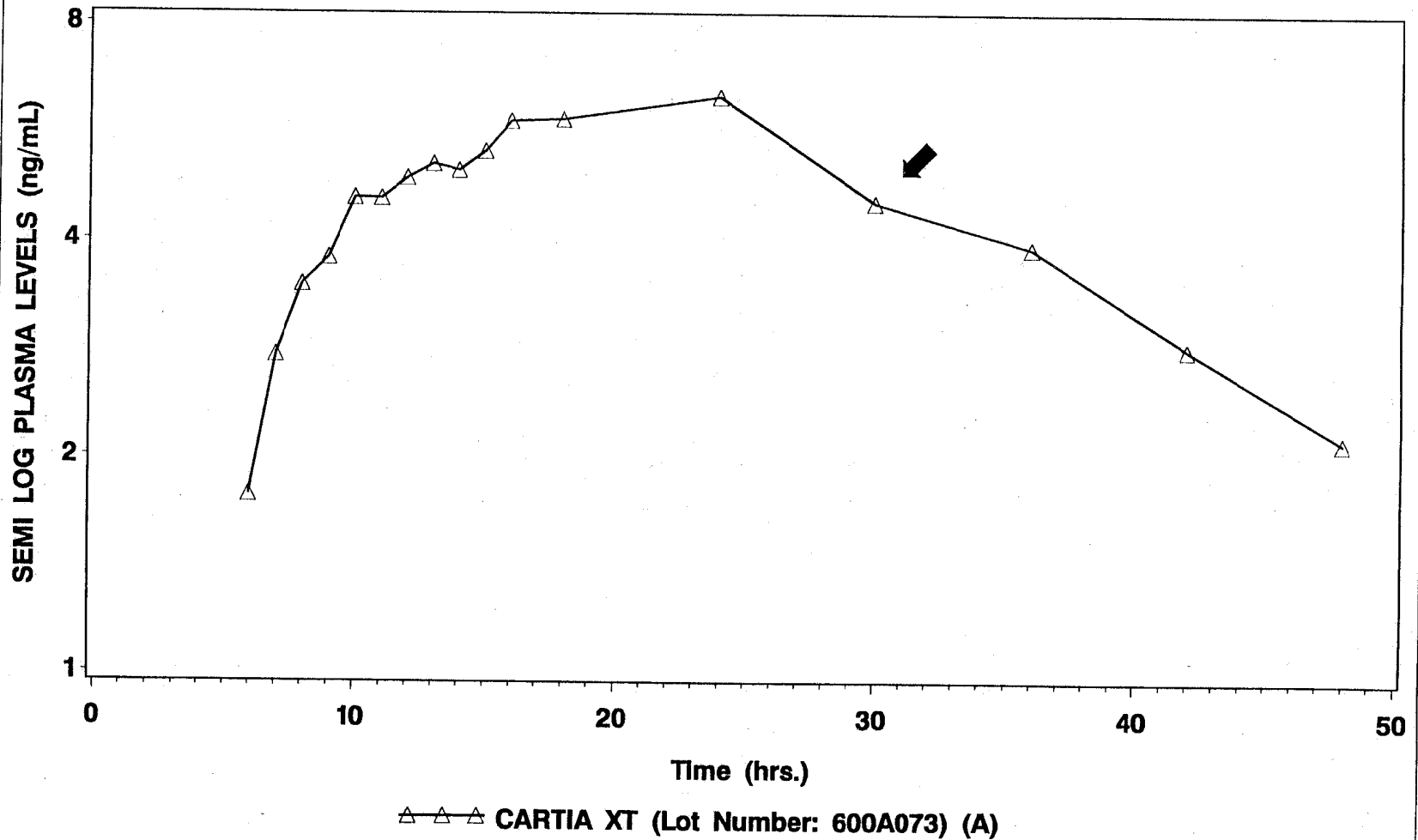


FIGURE 2.56

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 01

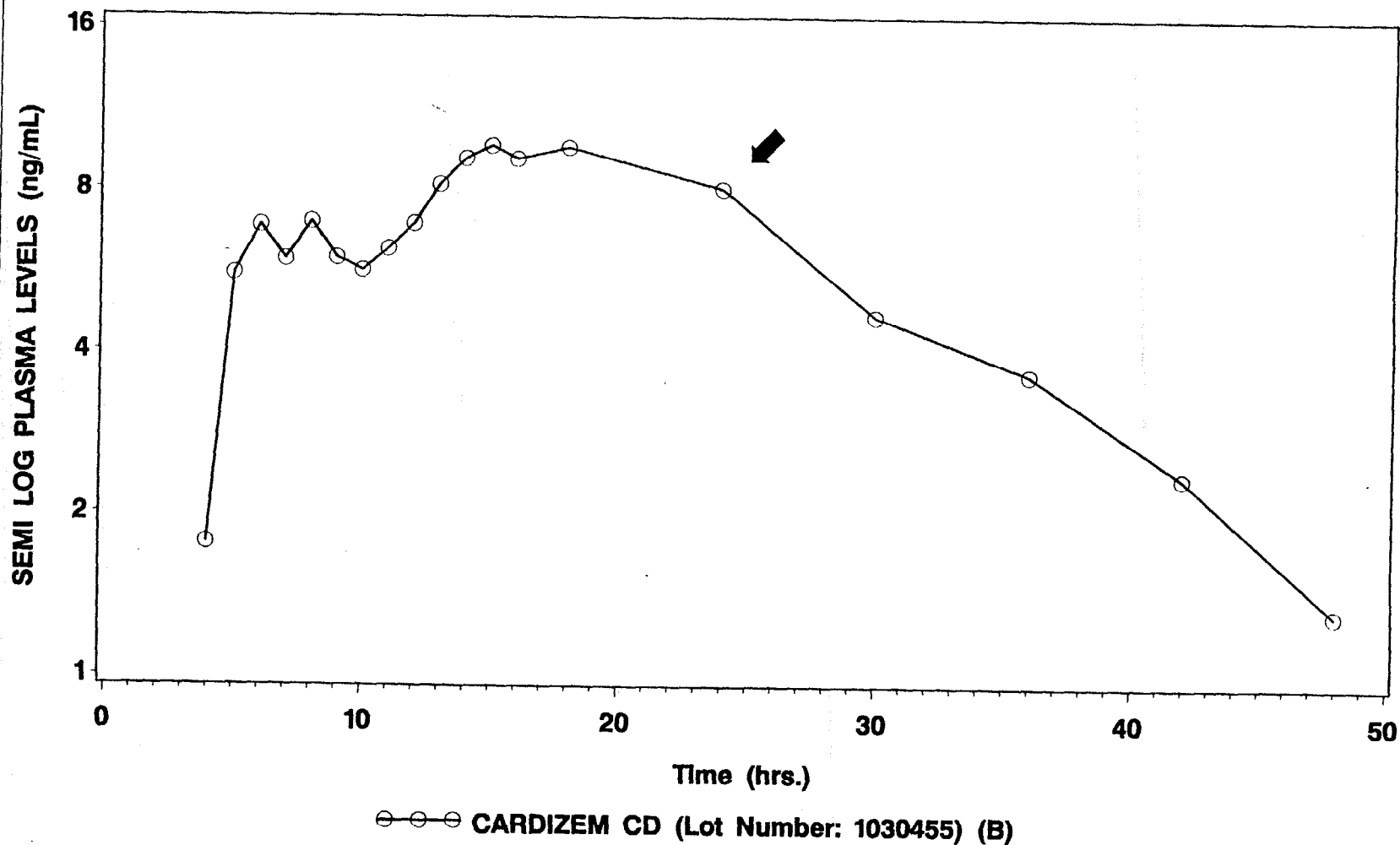


FIGURE 2.57

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 03

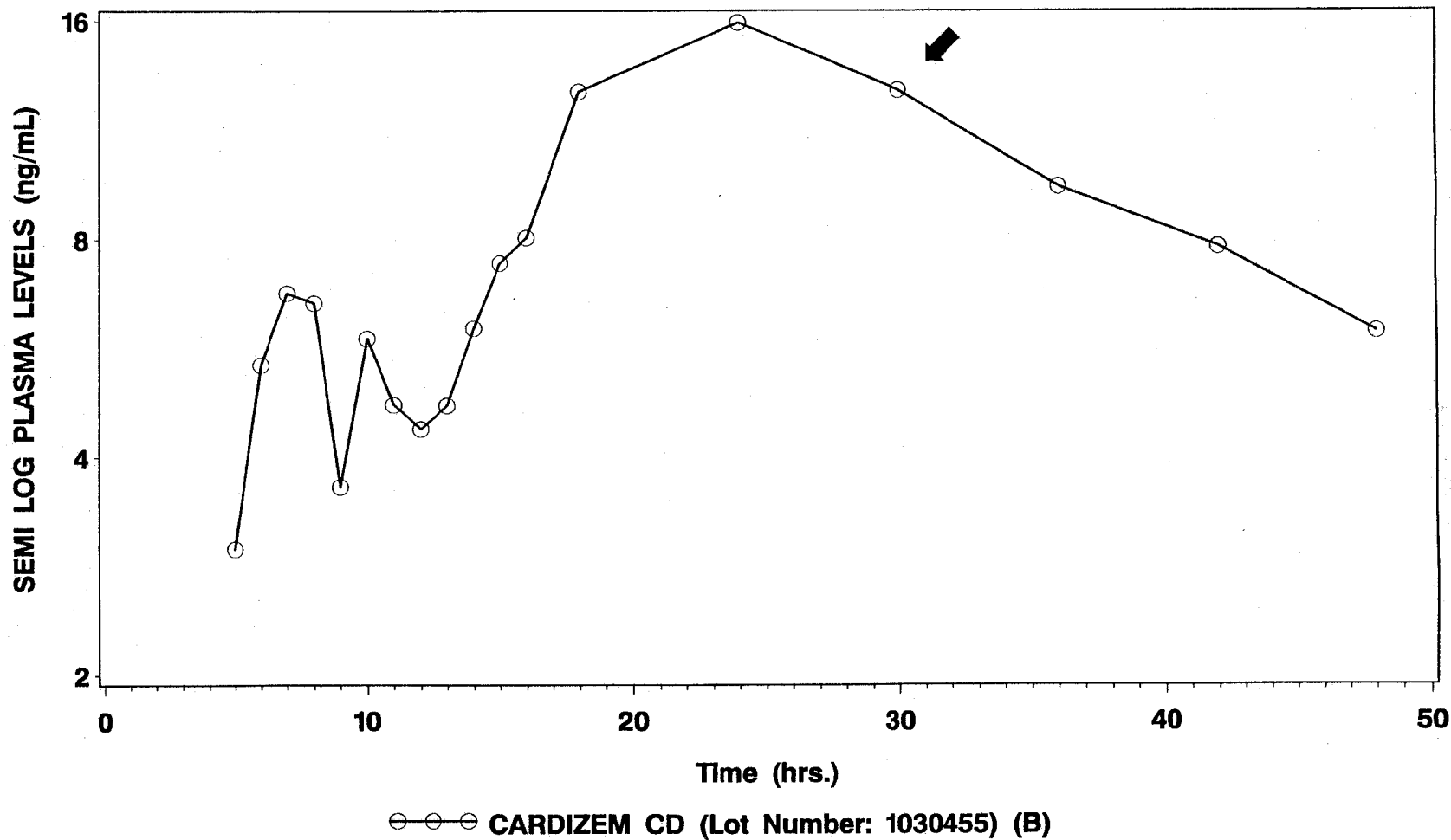


FIGURE 2.58

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 04

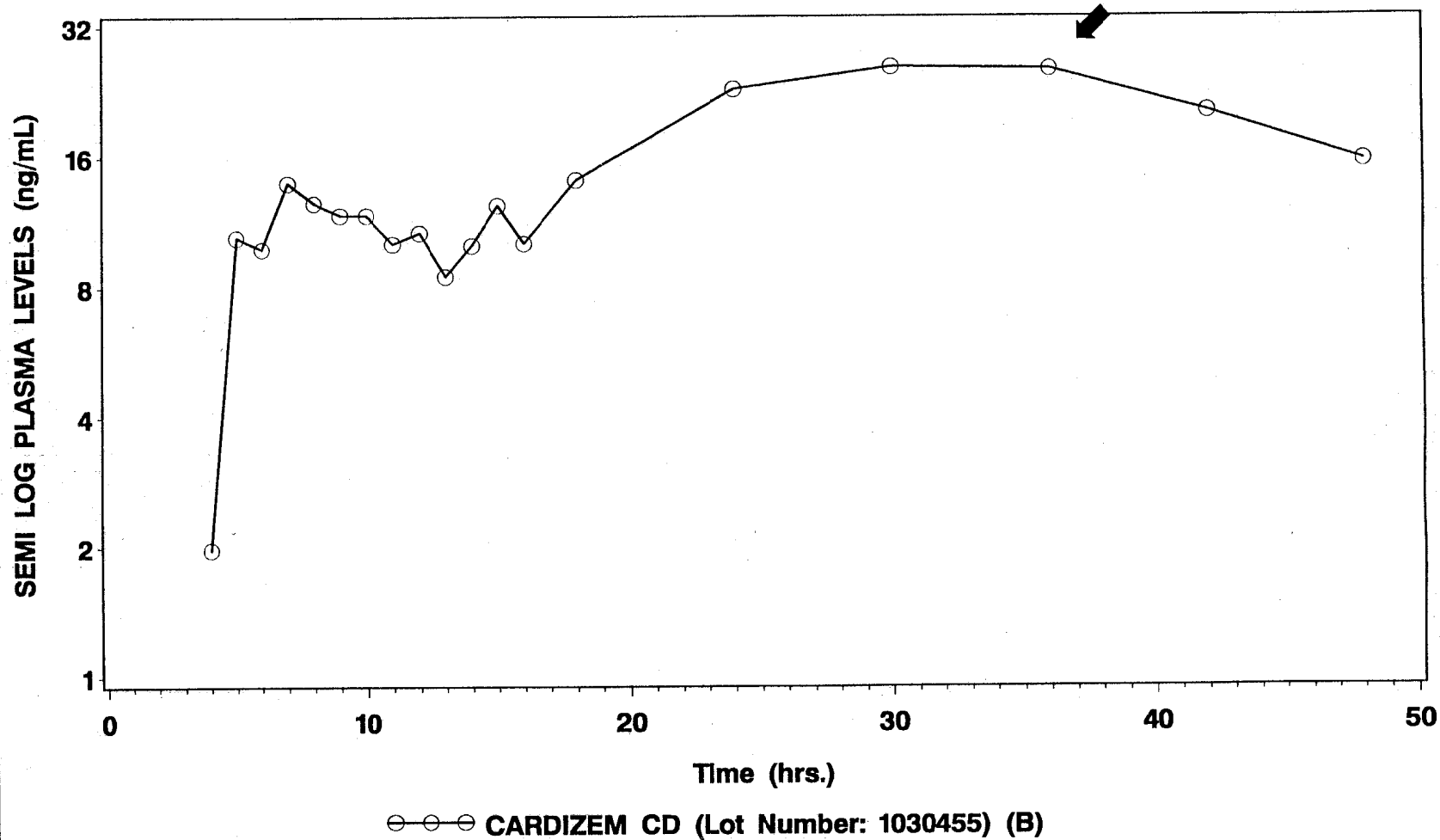
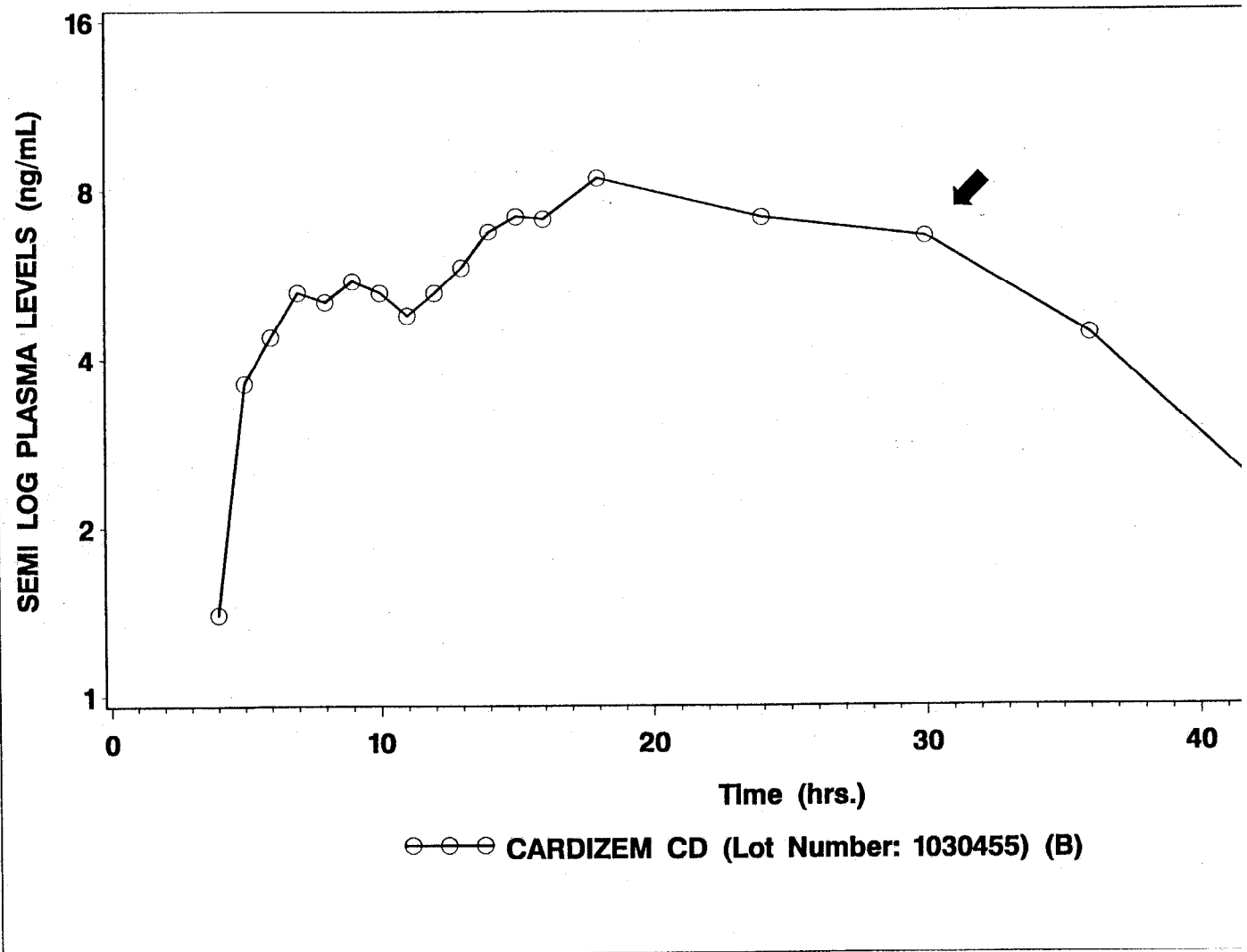


FIGURE 2.59

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (S1)
SUBJECT = 05



SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 06

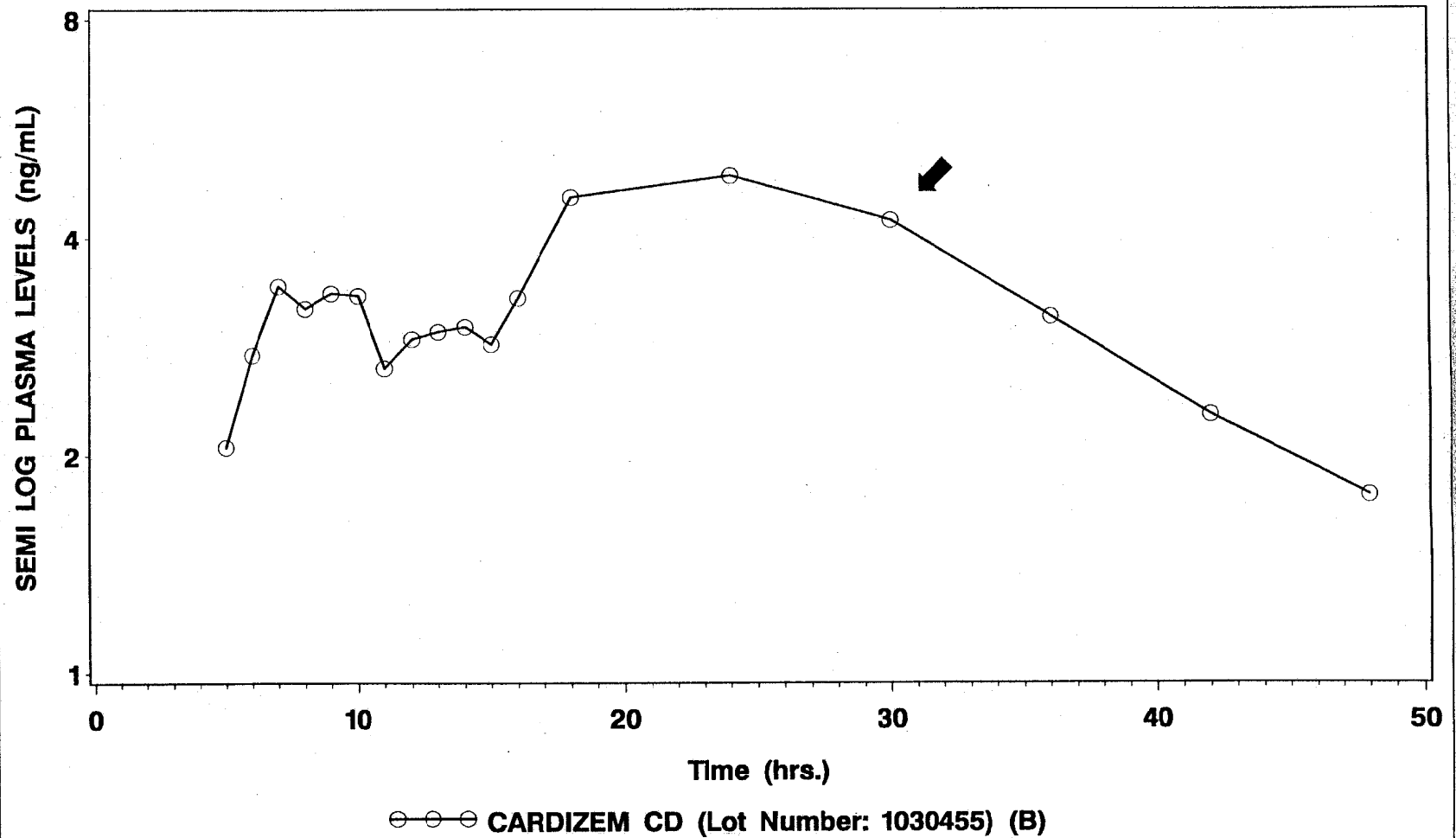


FIGURE 2.61

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 07

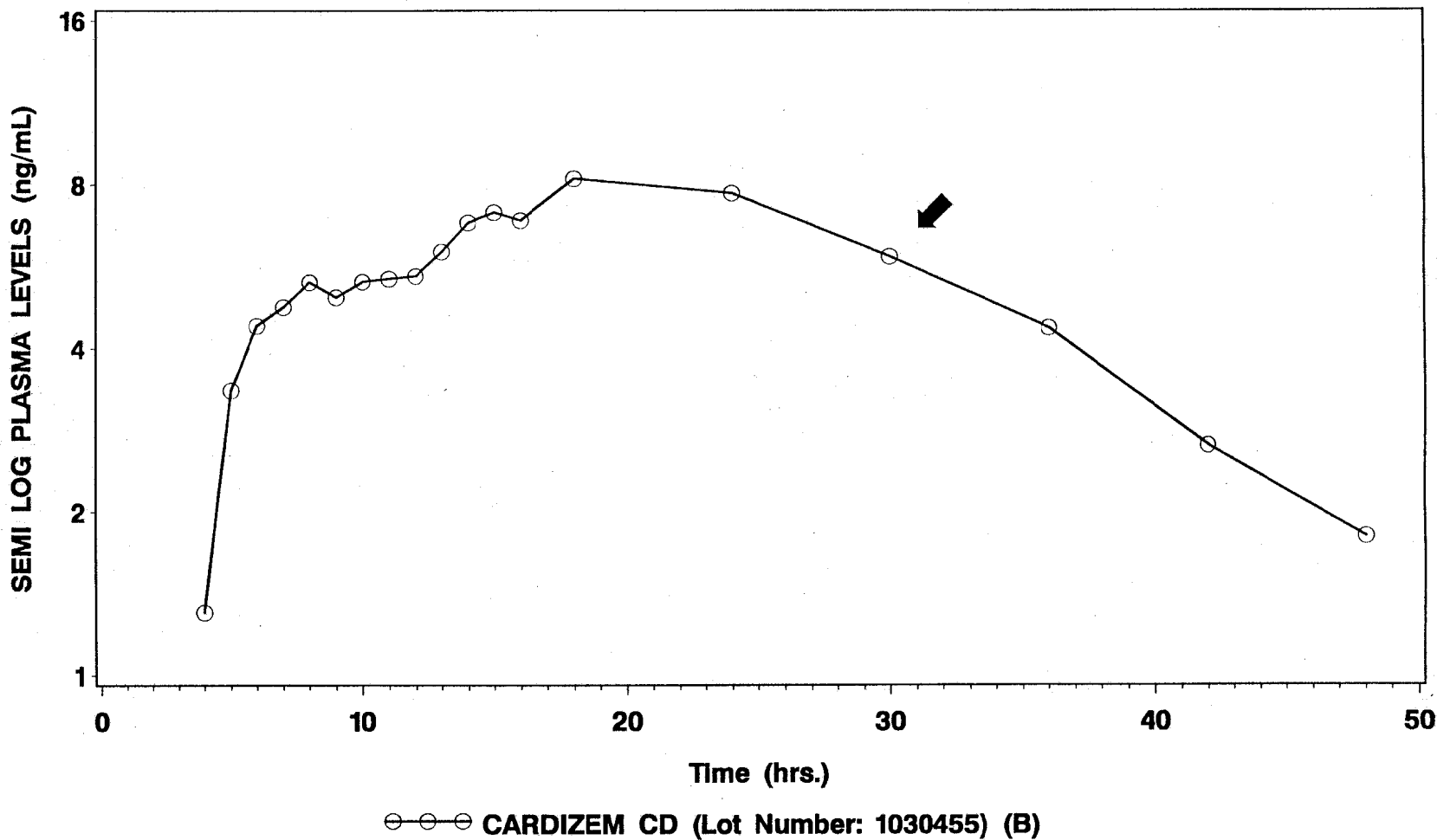


FIGURE 2.62

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 08

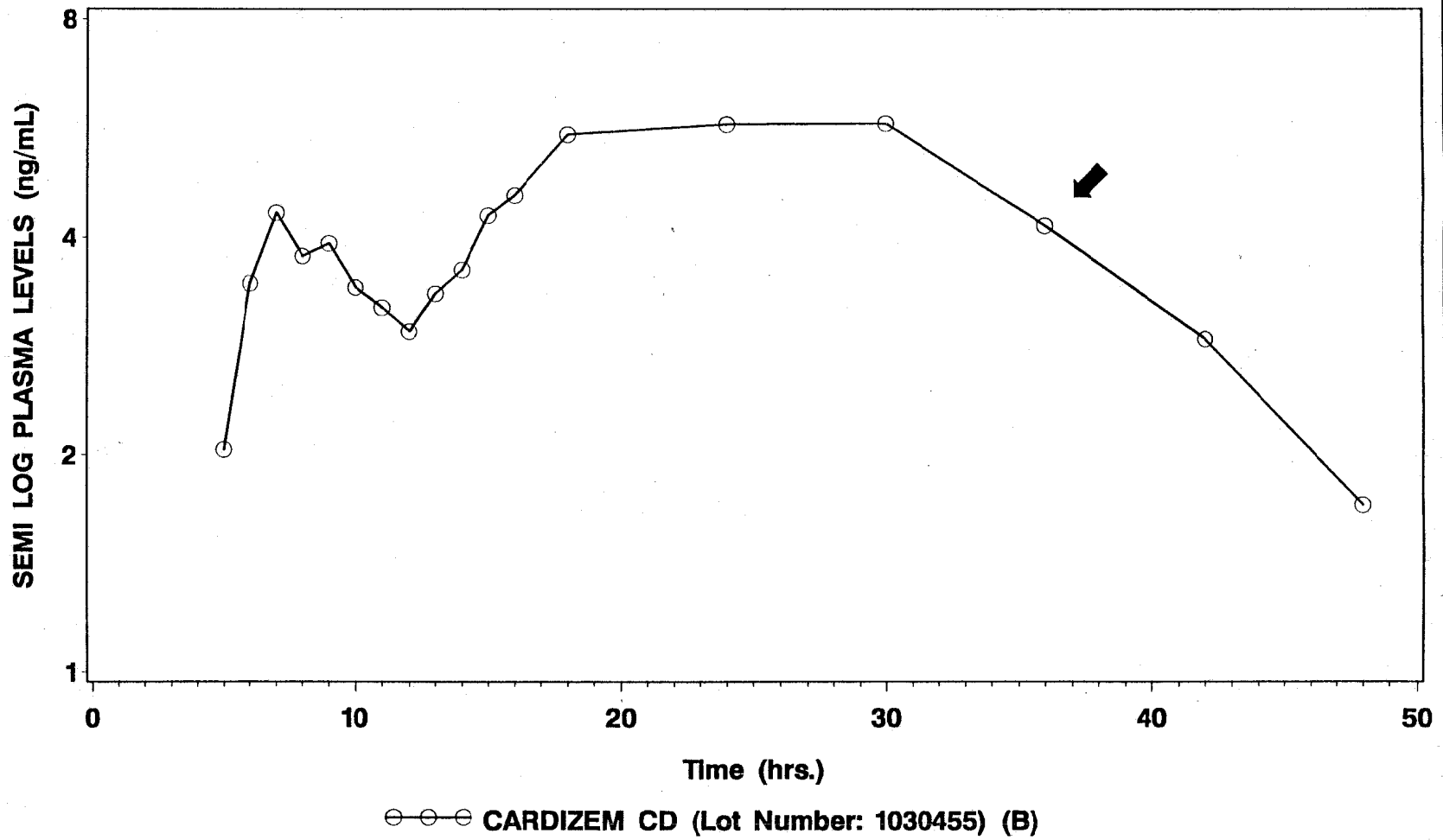
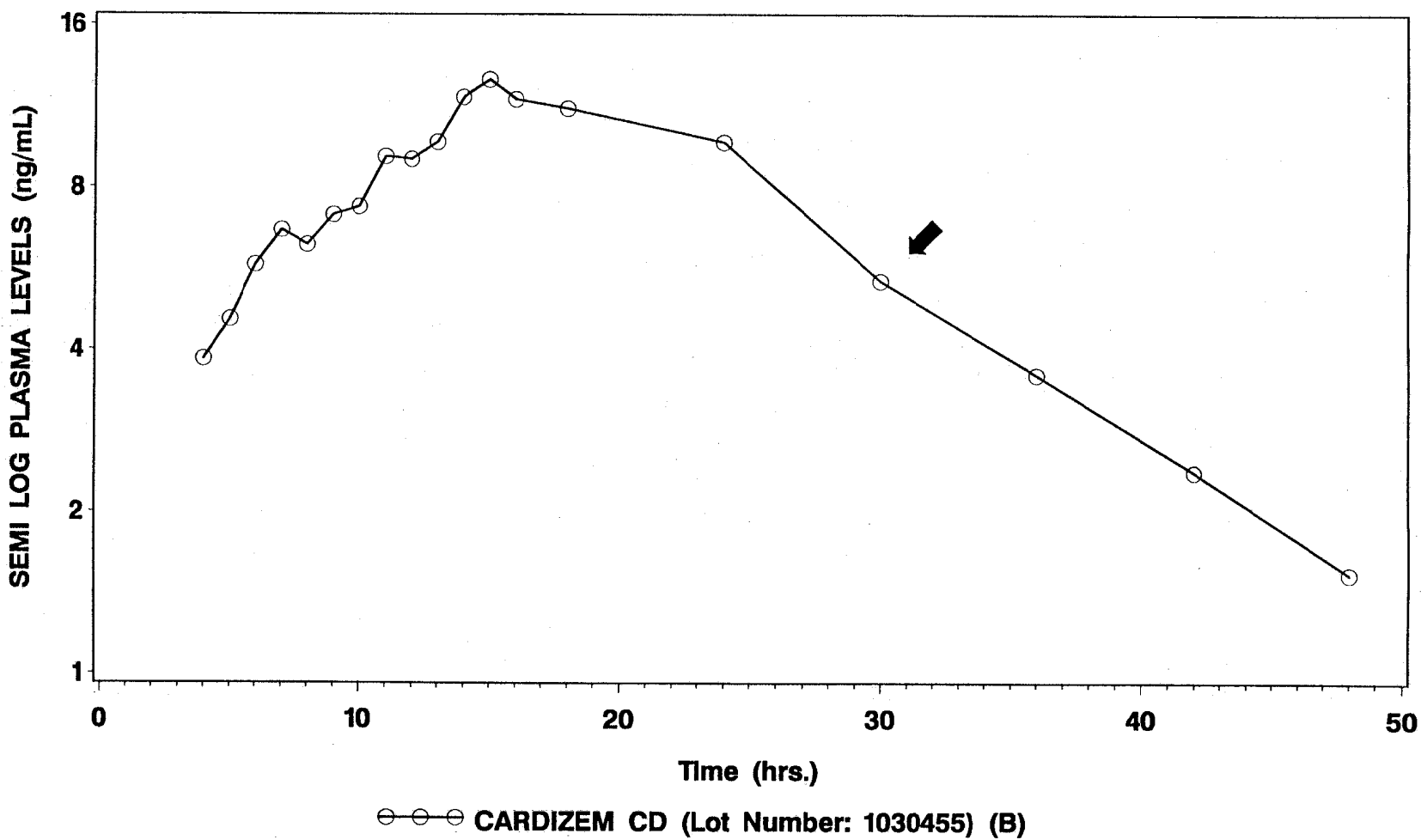


FIGURE 2.63

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 09



○—○—○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 2.64

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT=10

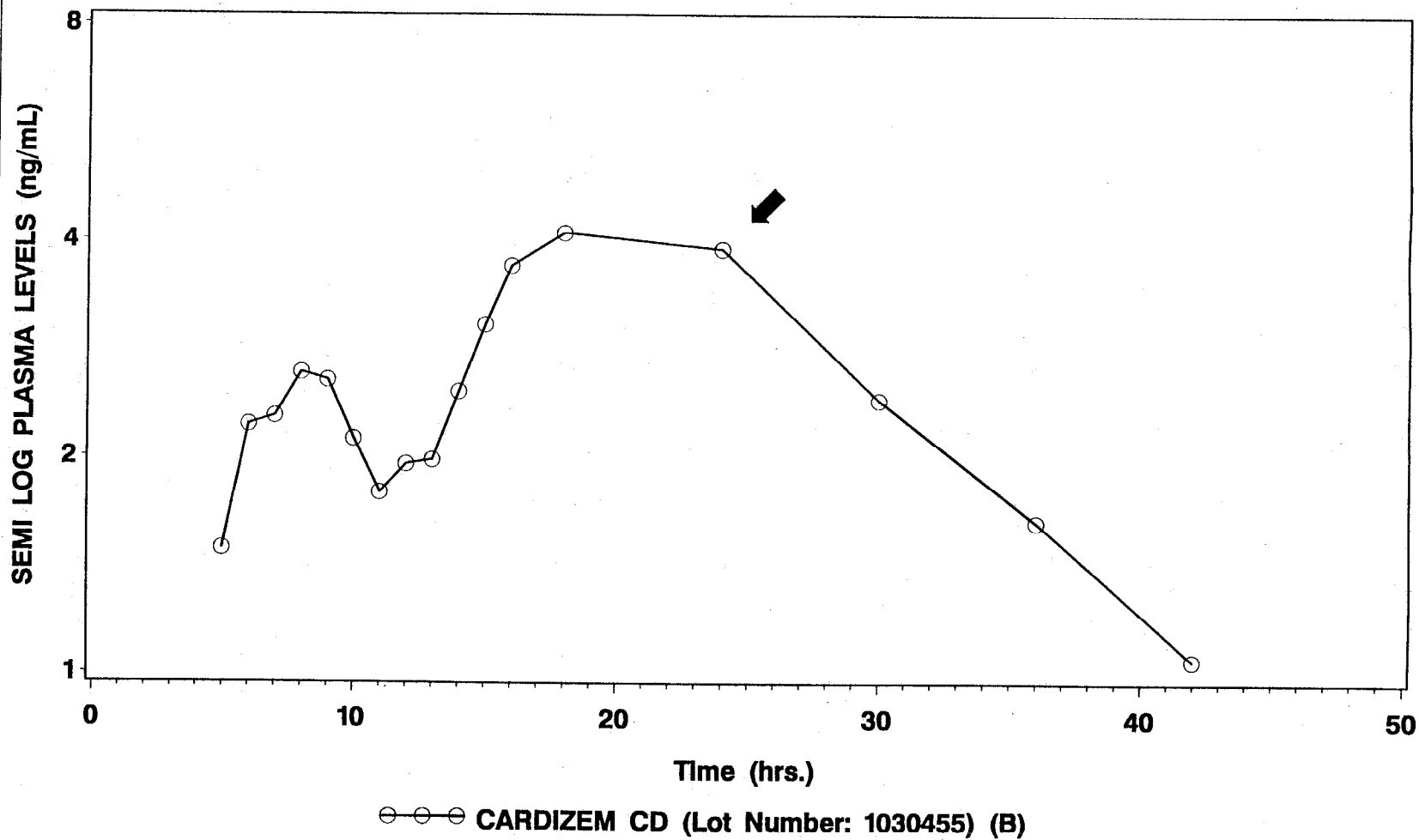


FIGURE 2.65

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 11

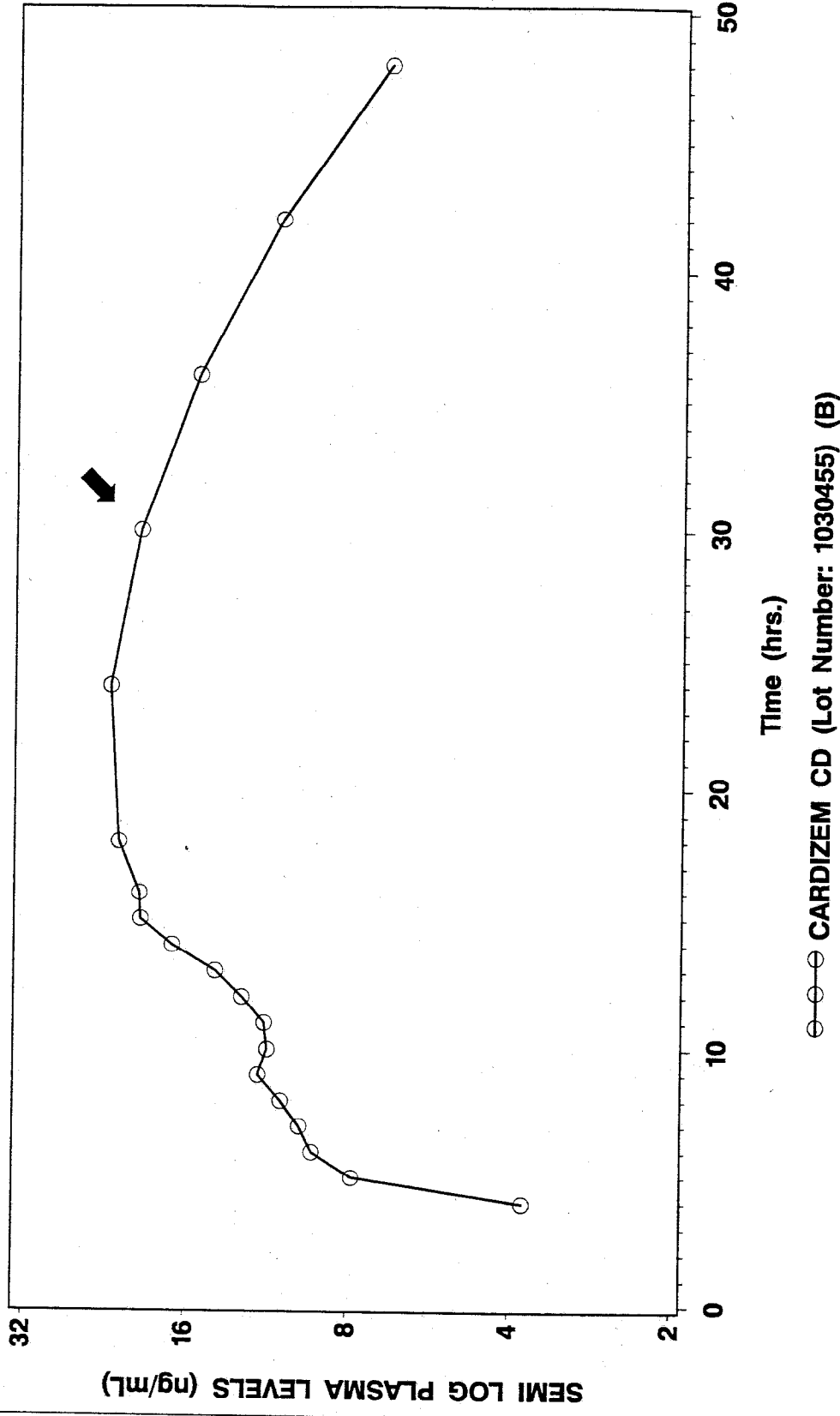


FIGURE 2.66

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 12

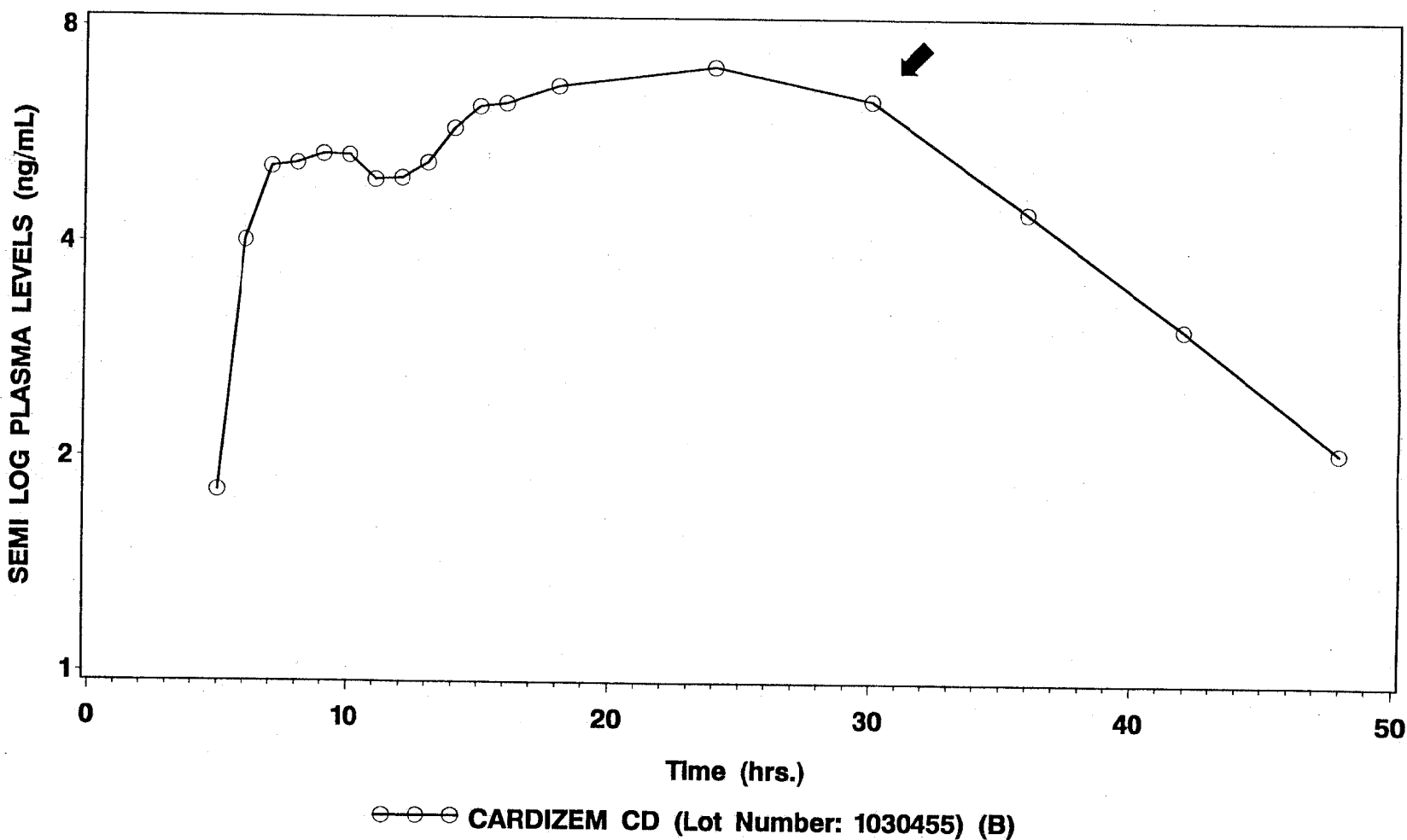
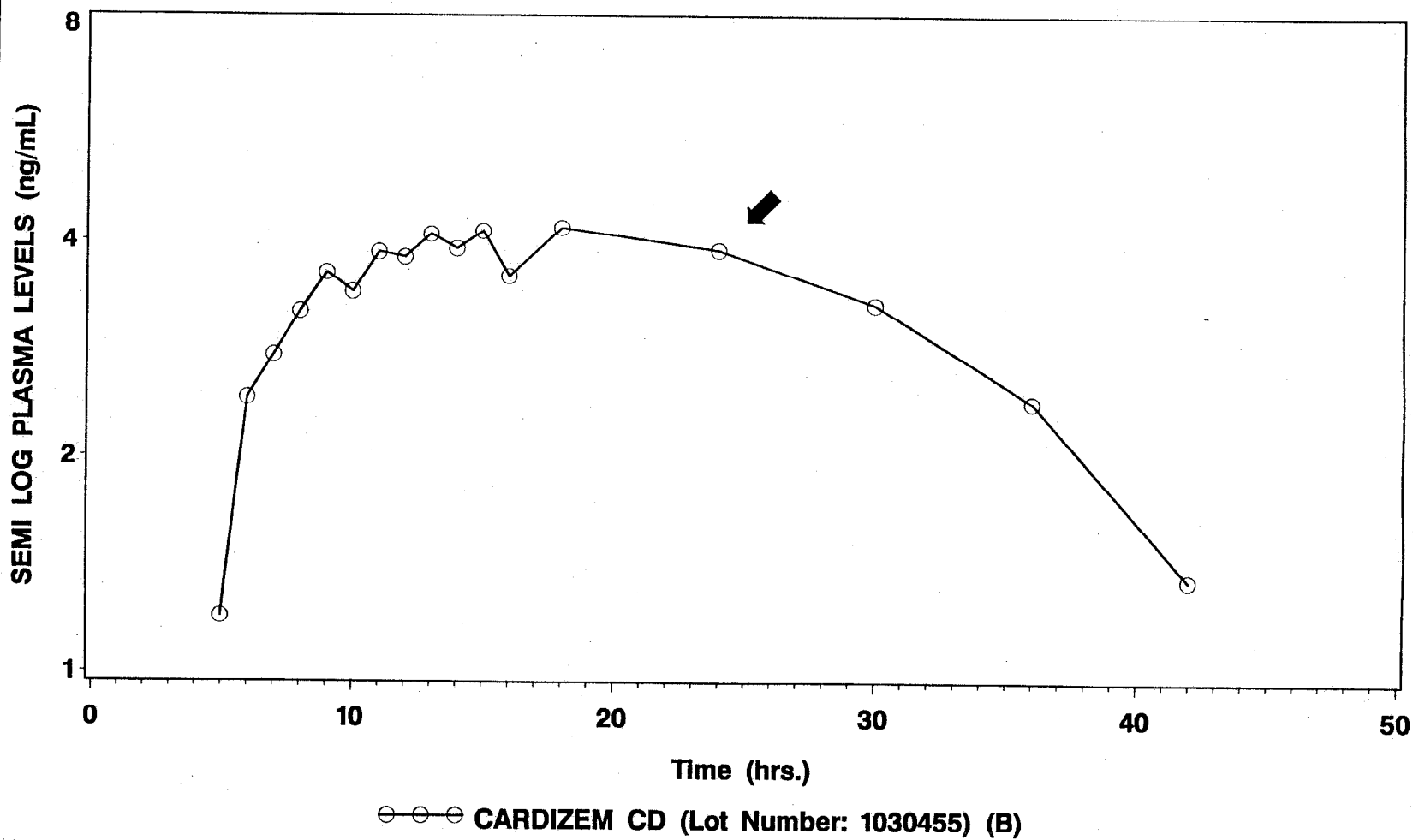


FIGURE 2.67

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 13



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 2.68

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 14

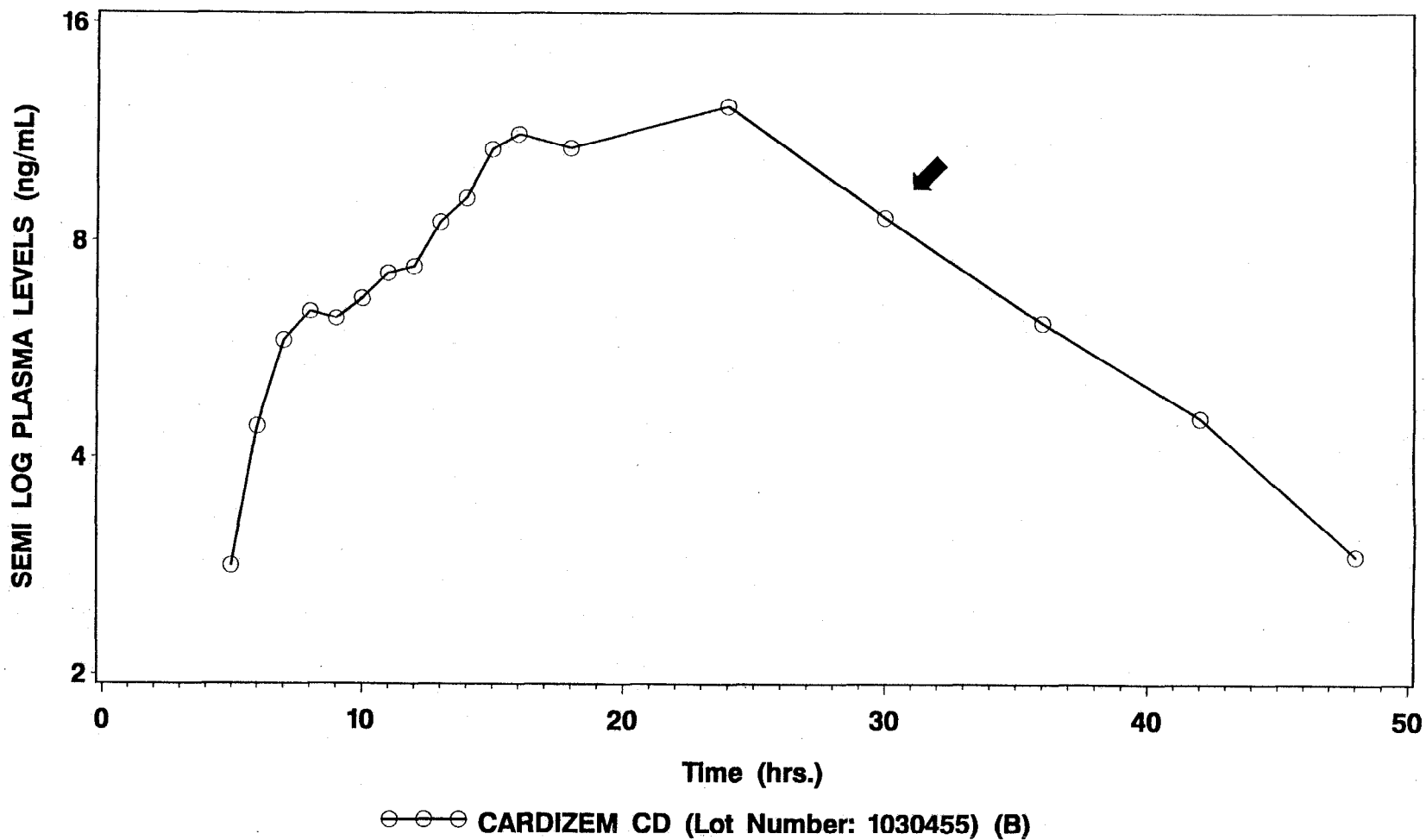


FIGURE 2.69

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 15

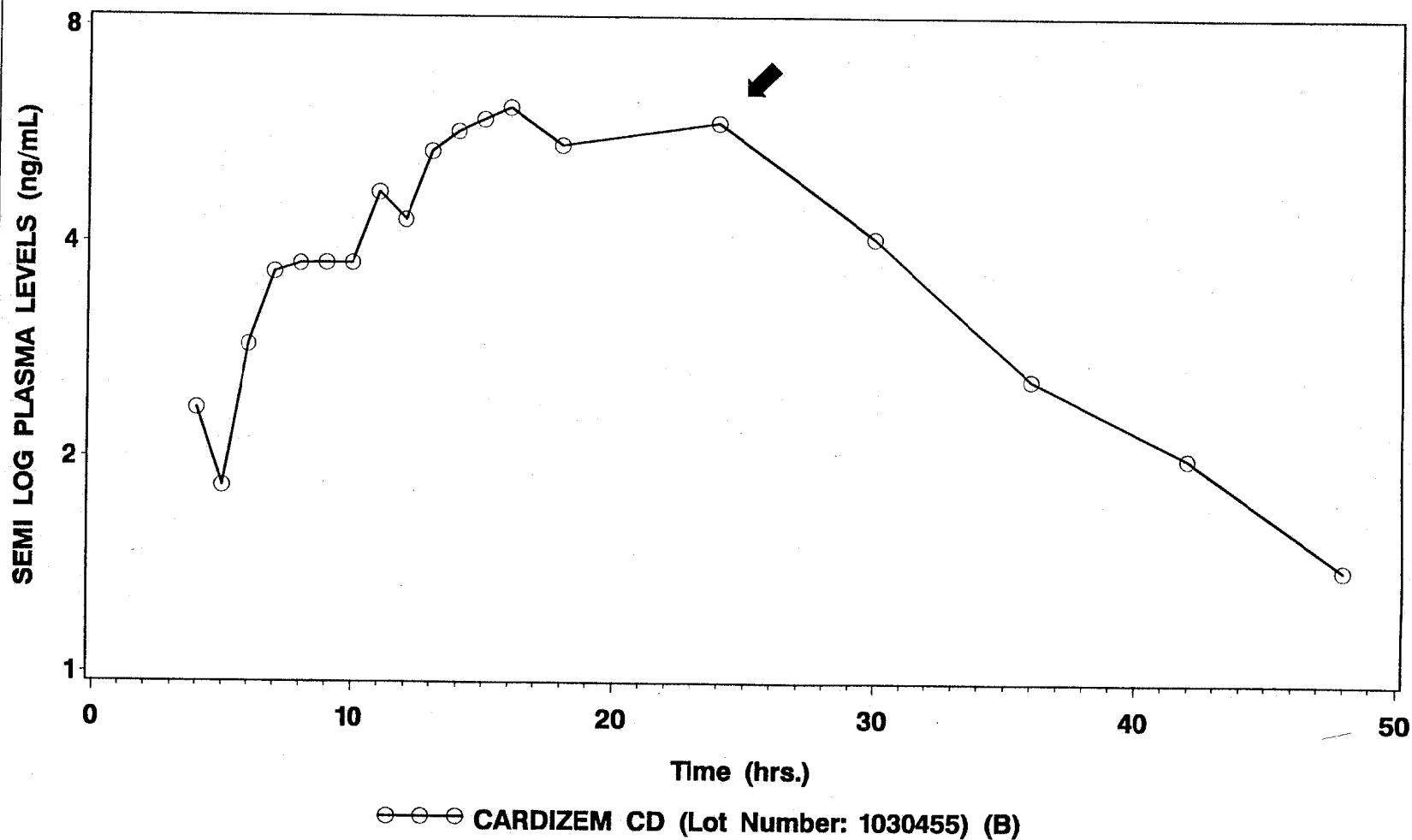


FIGURE 2.70

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 16

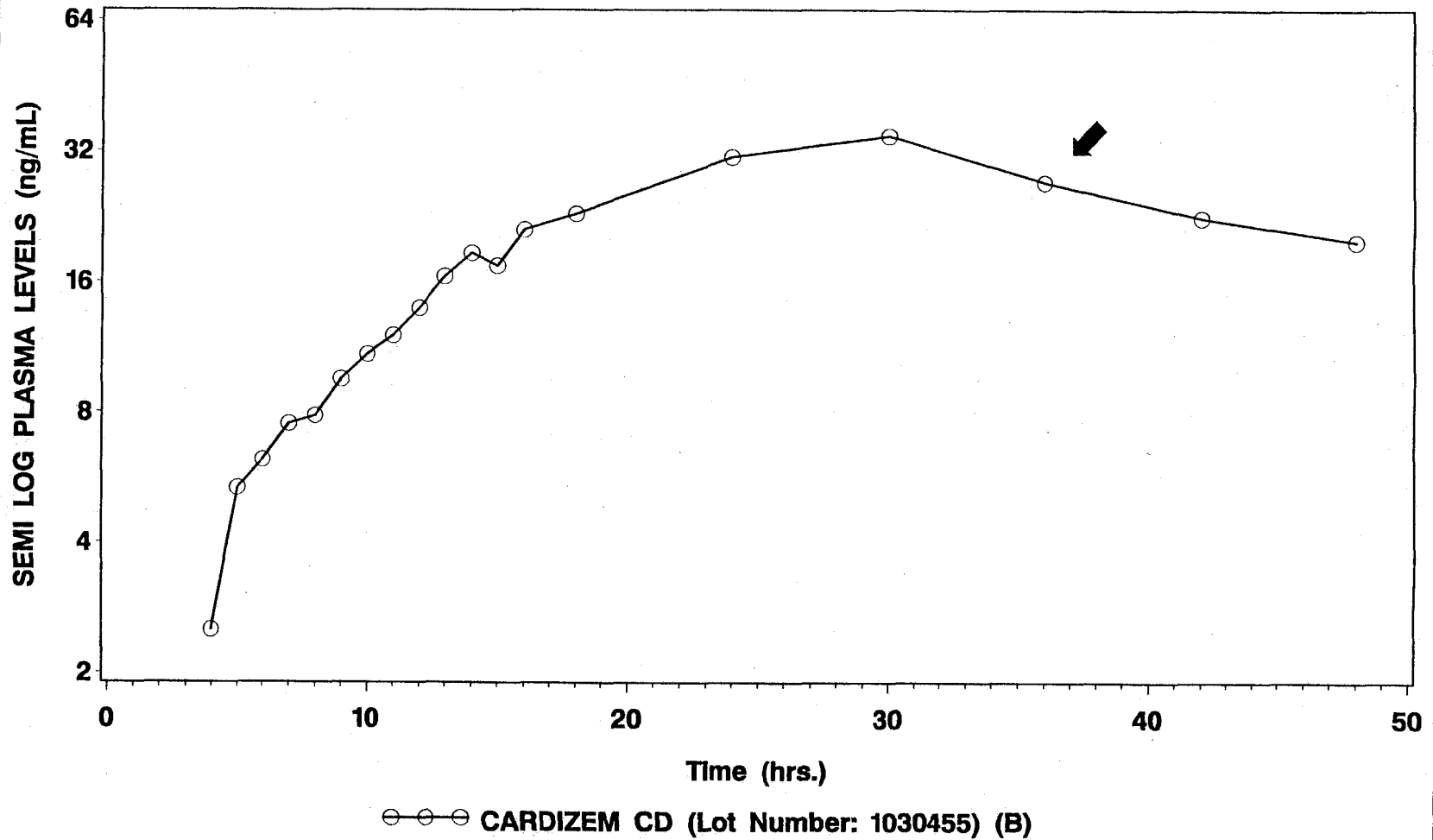
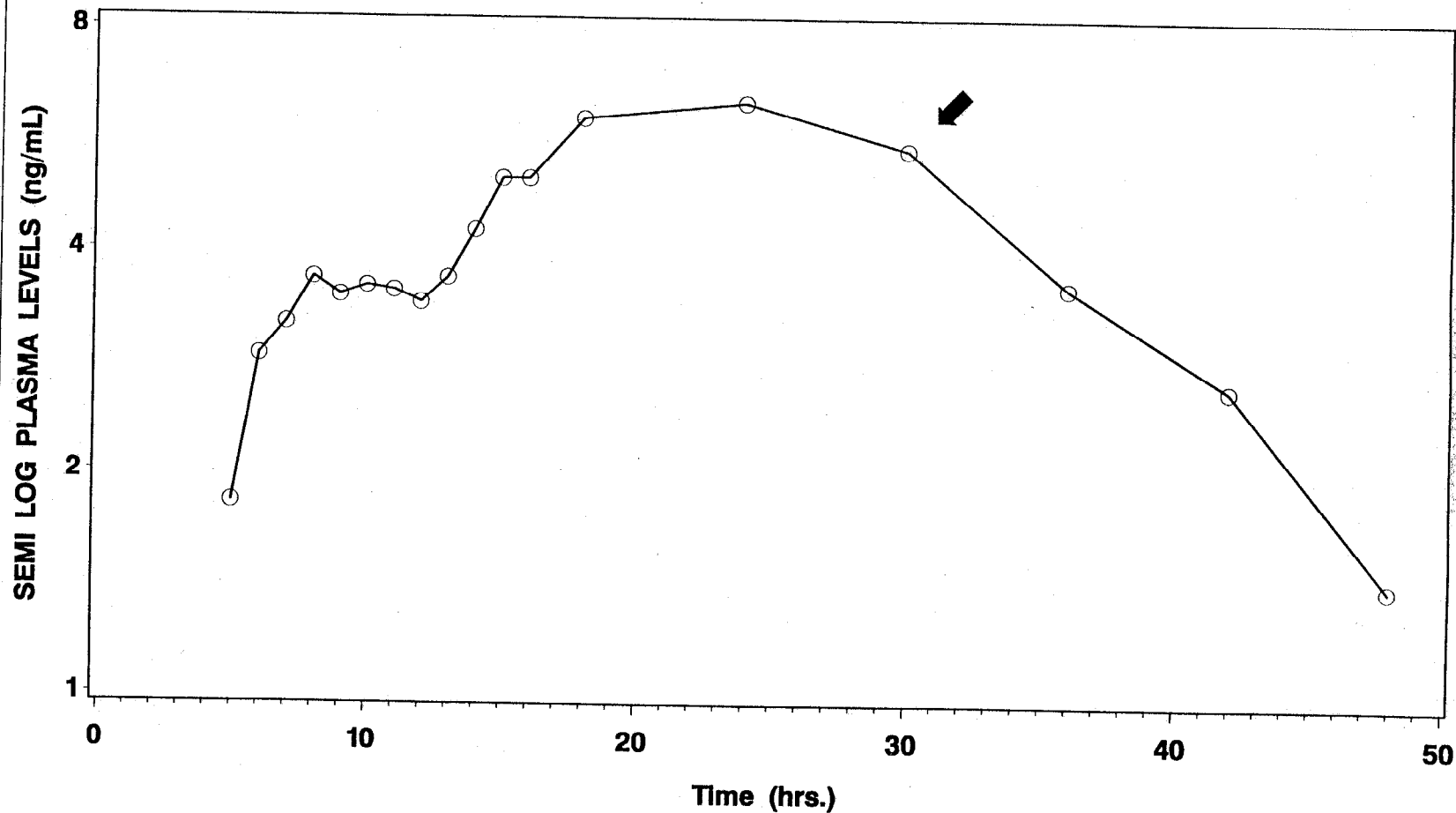


FIGURE 2.71

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 17



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 2.72

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 18

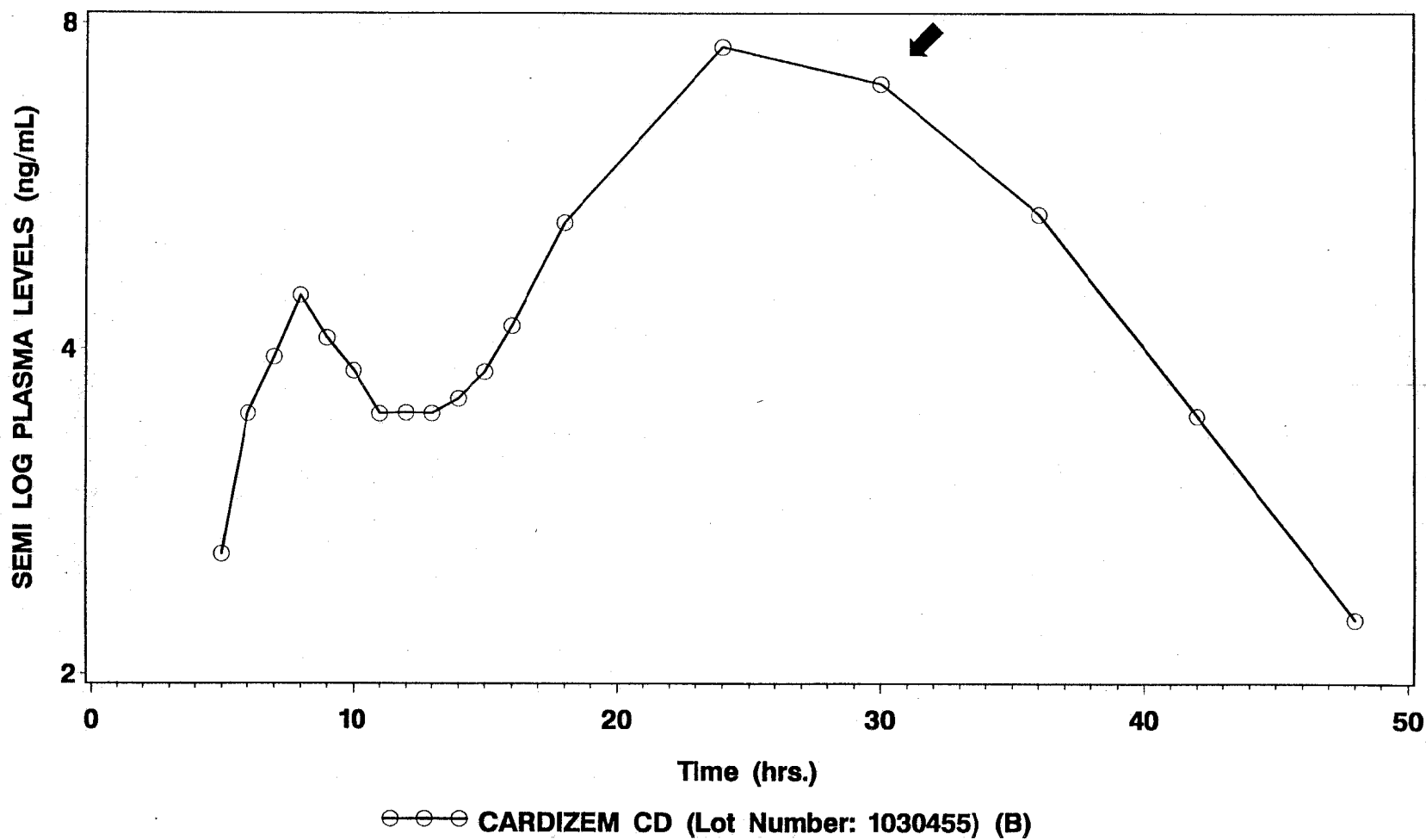


FIGURE 2.73

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 19

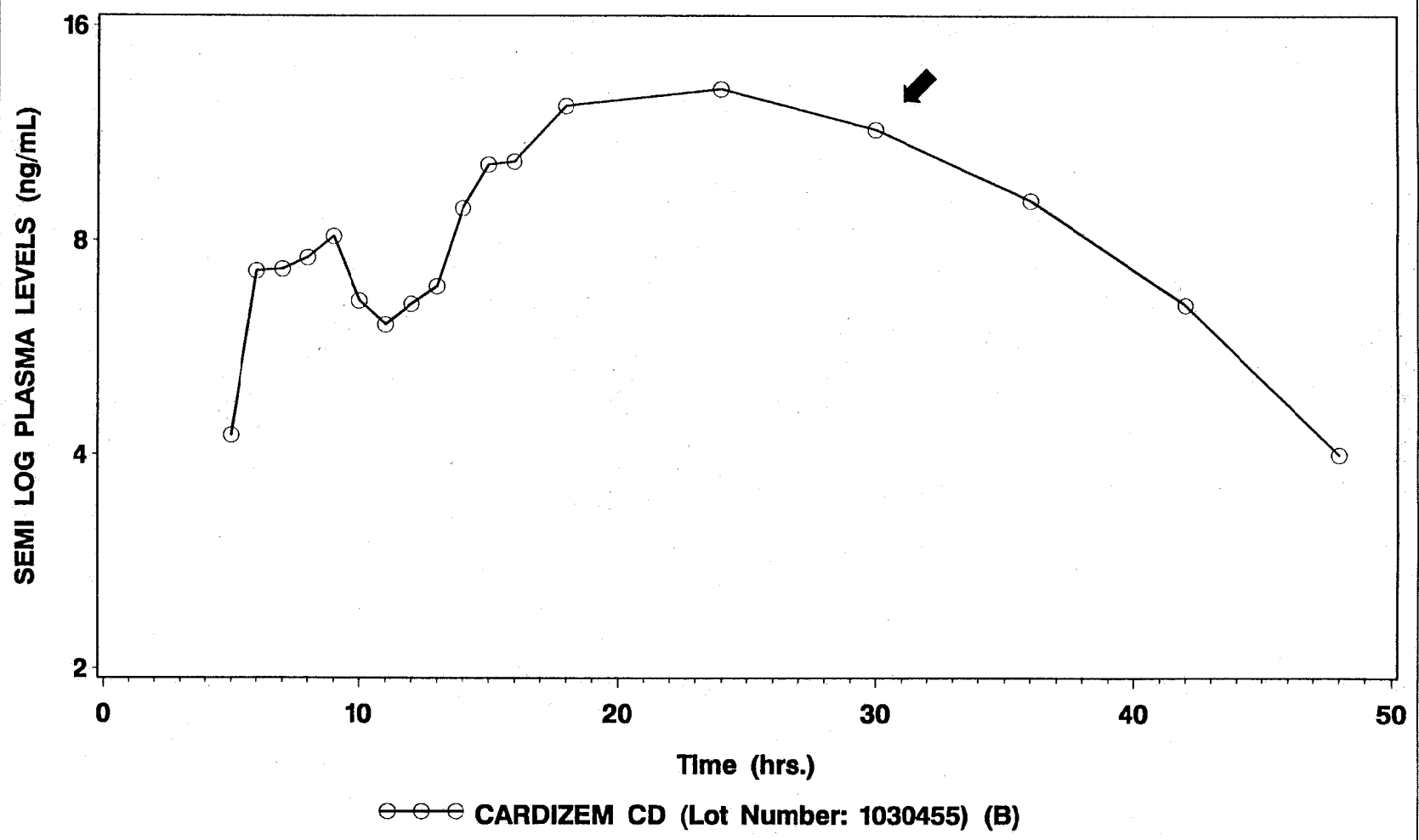


FIGURE 2.74

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 20

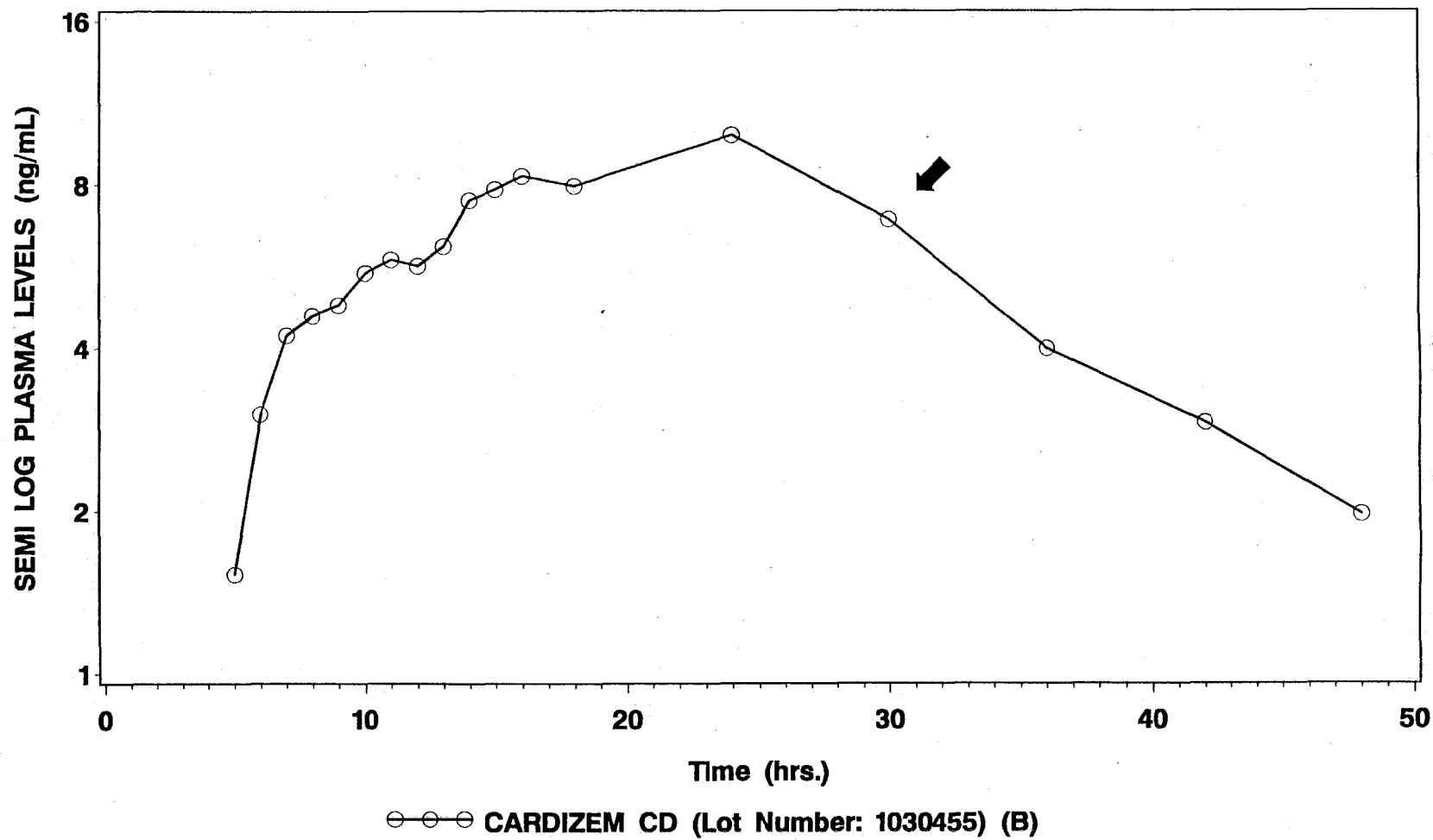


FIGURE 2.75

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 21

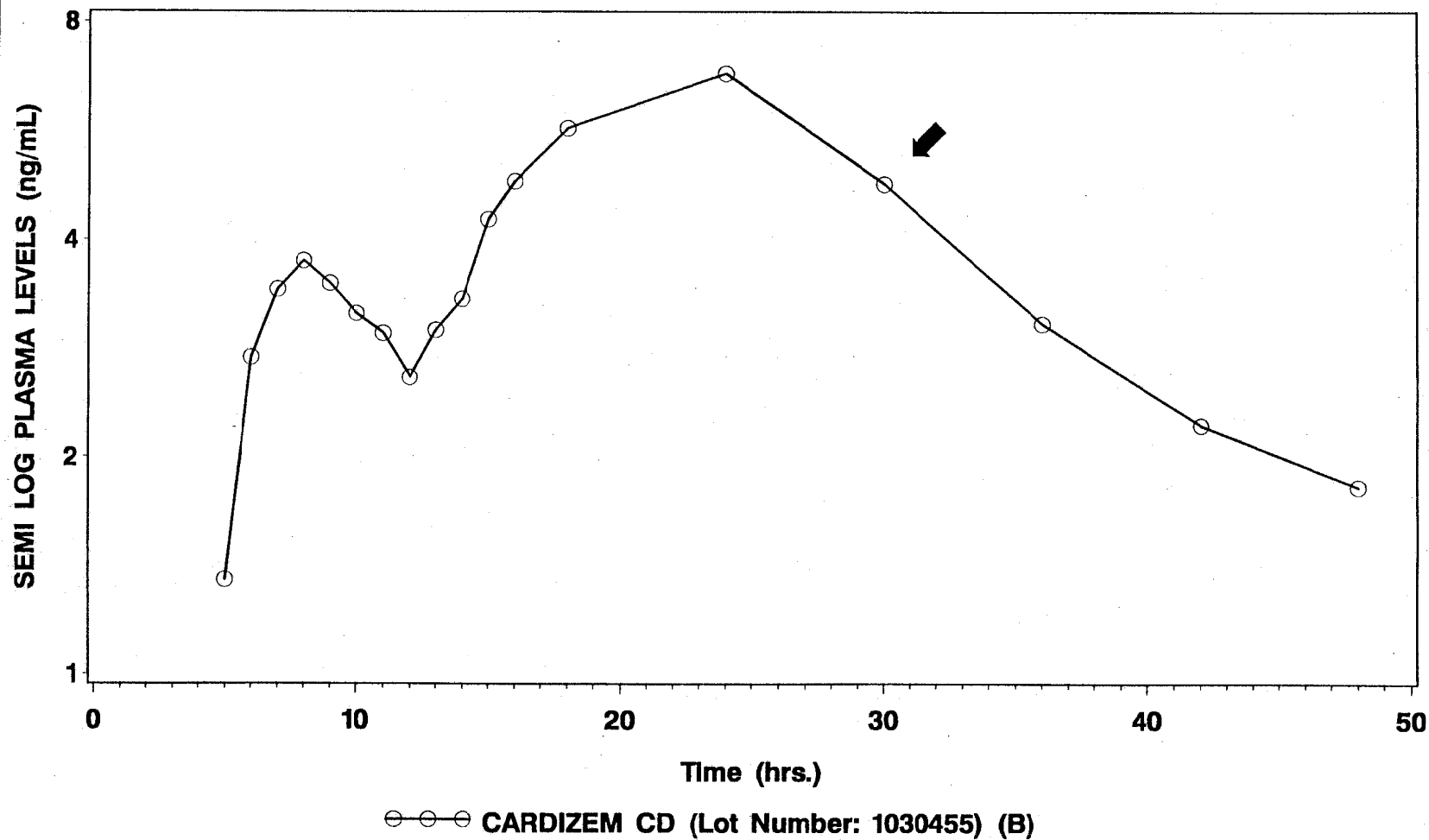


FIGURE 2.76

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 22

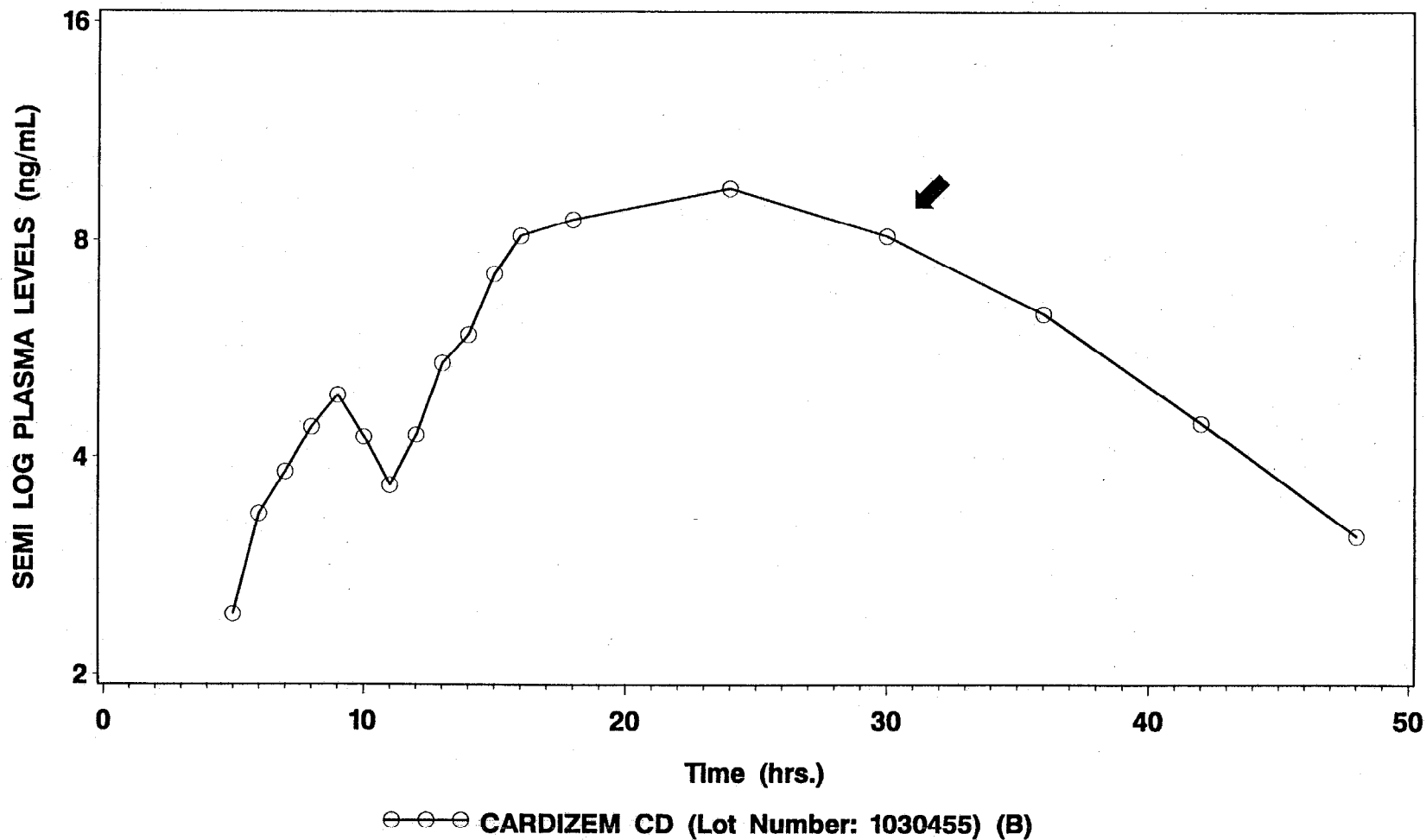


FIGURE 2.77

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 23

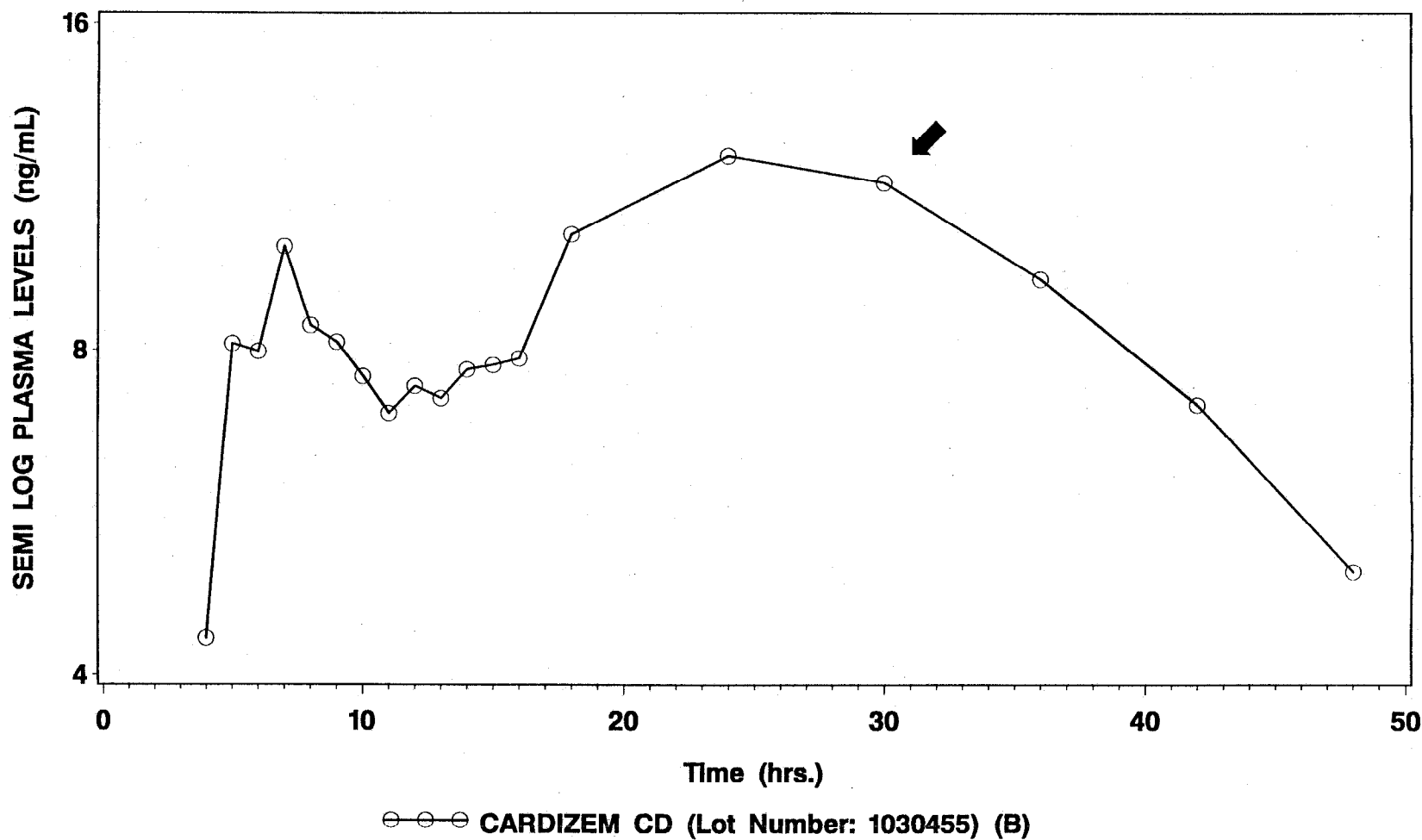
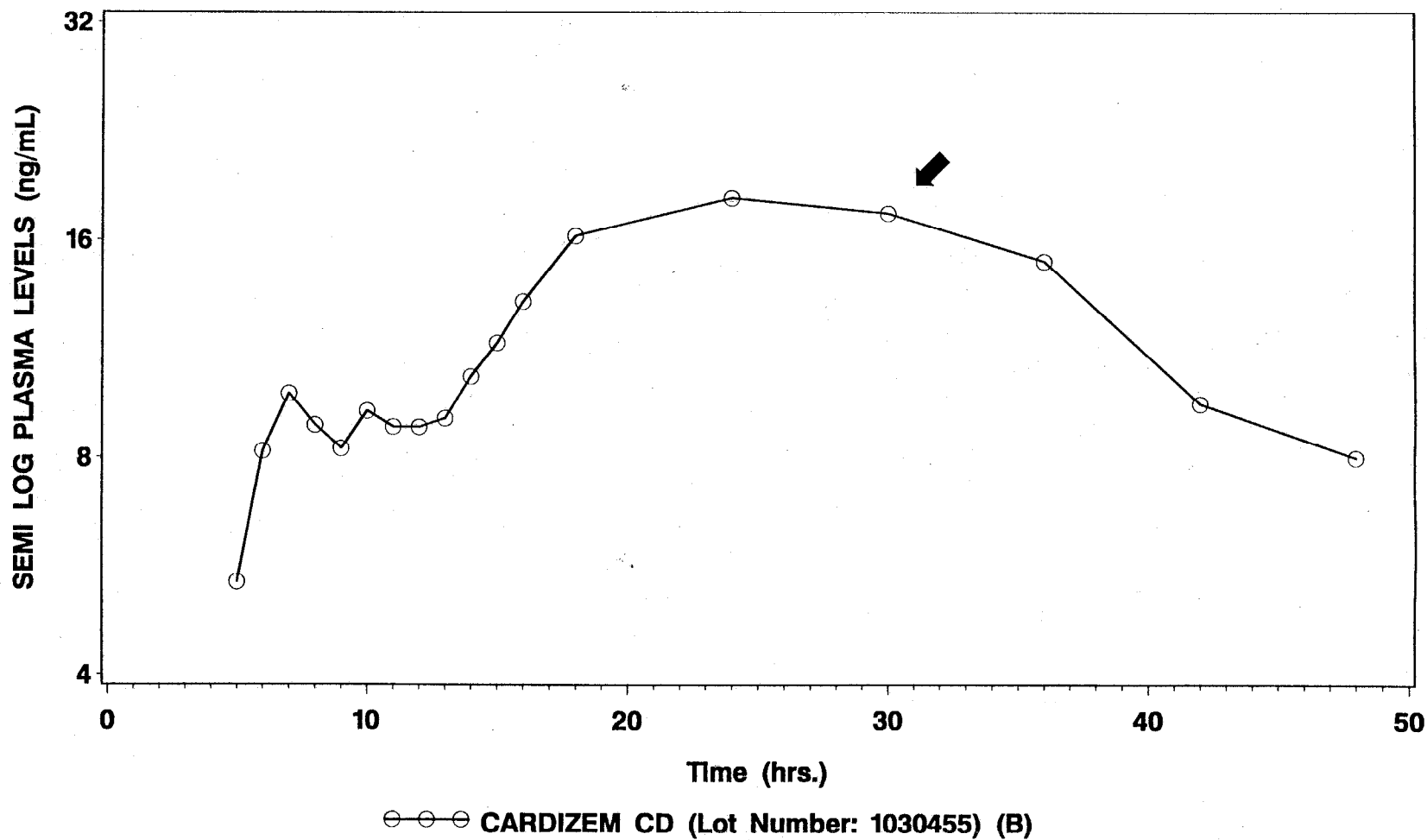


FIGURE 2.78

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 24



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 2.79

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 25

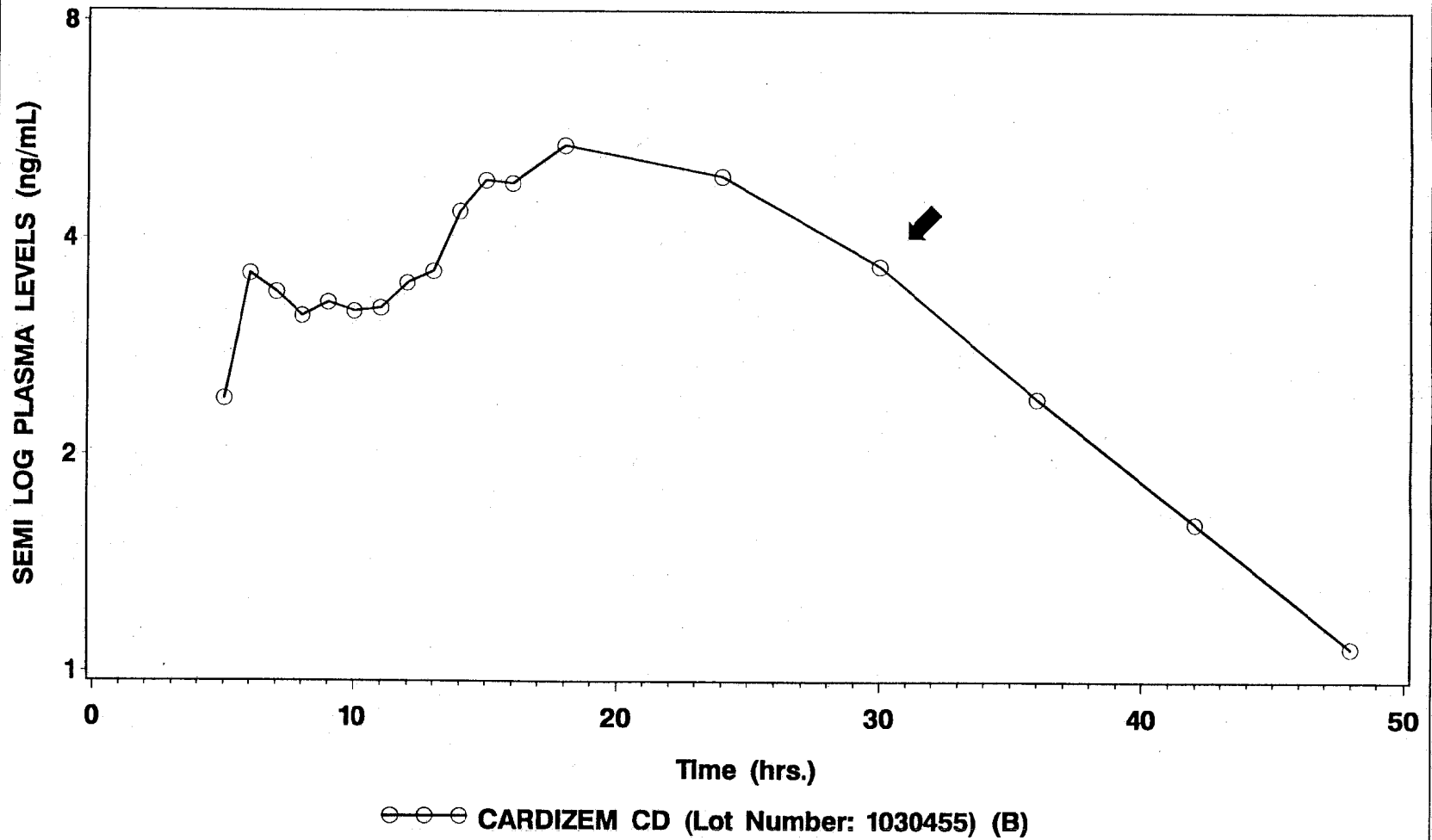


FIGURE 2.80

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 26

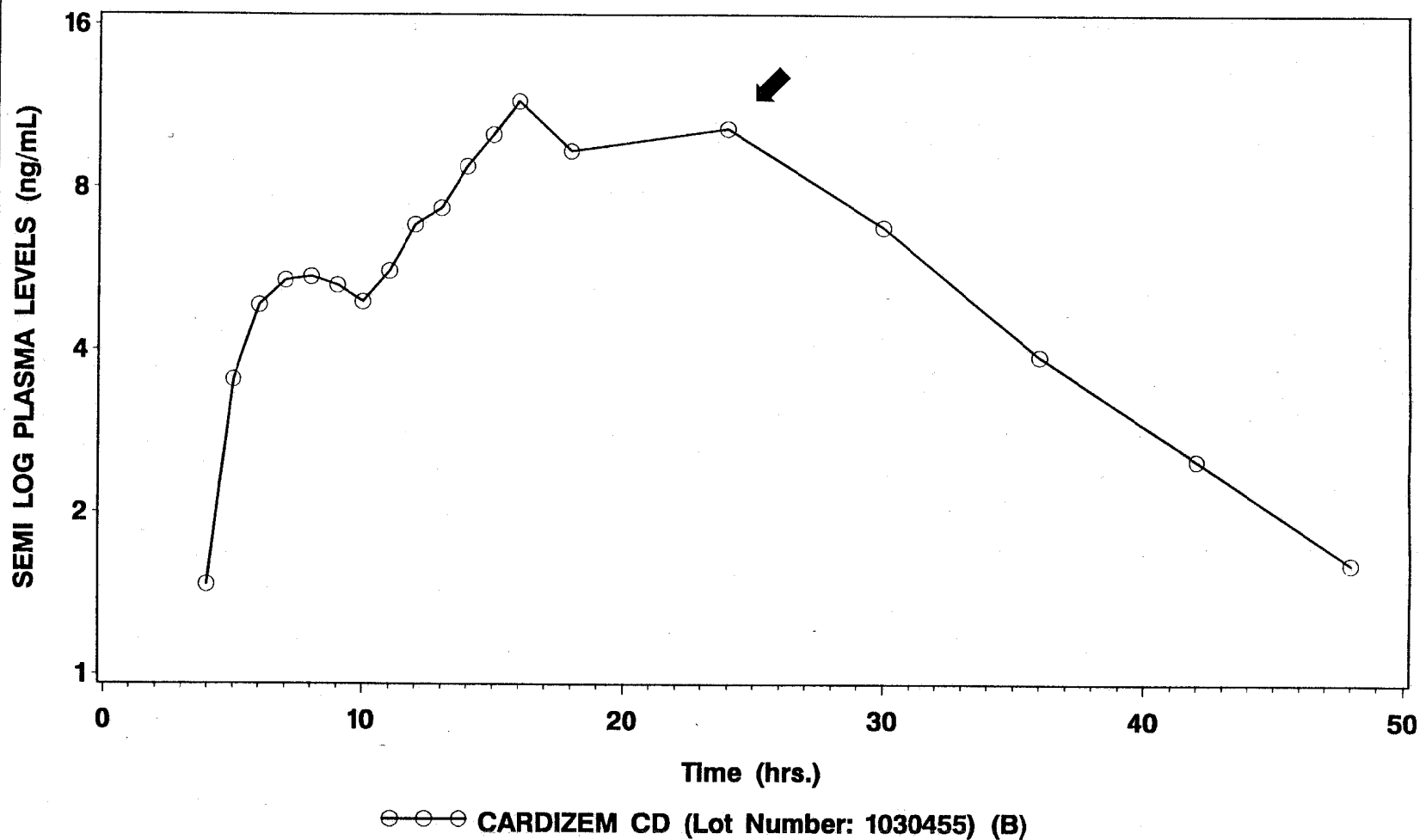


FIGURE 2.81

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 27

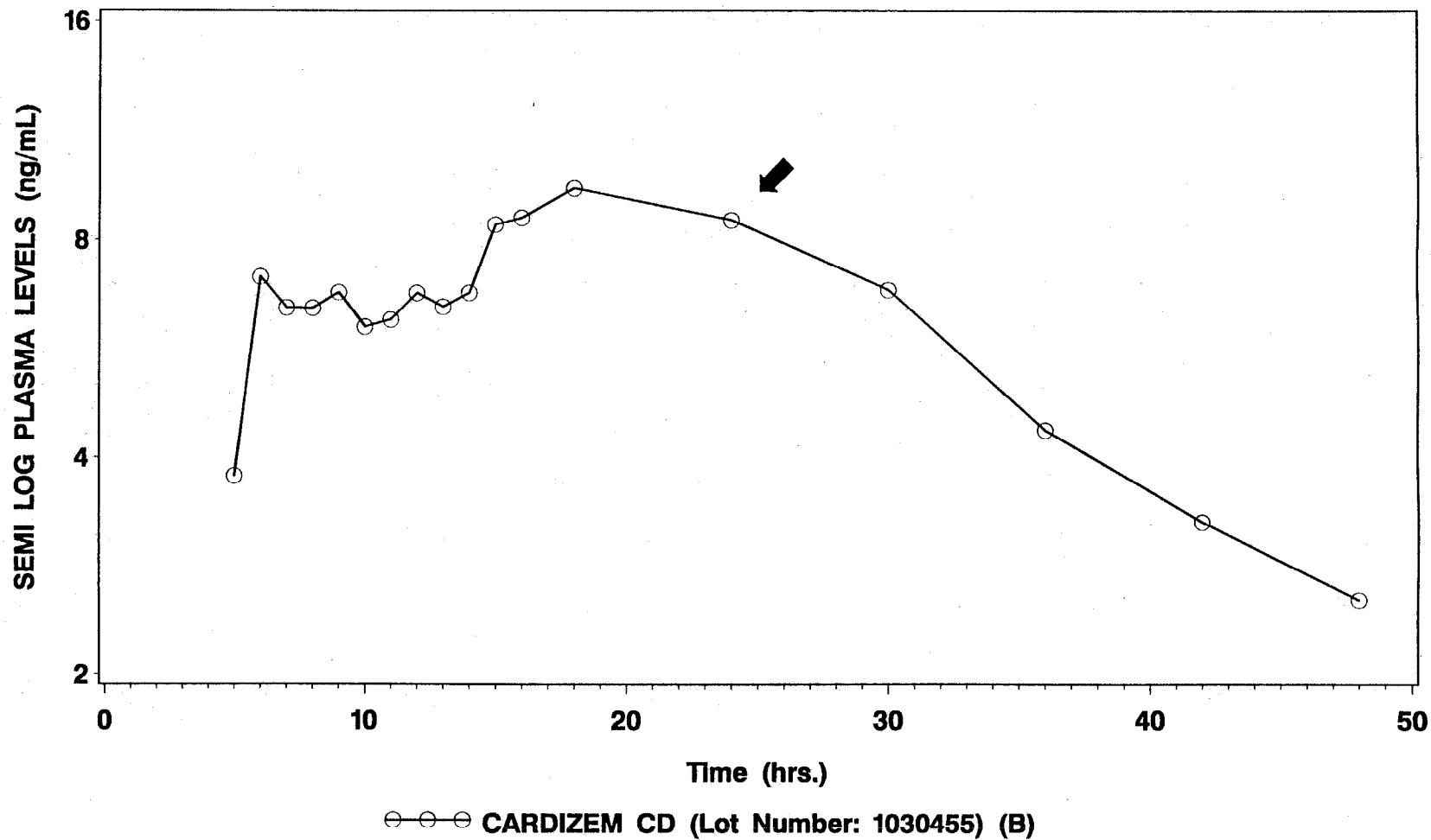


FIGURE 2.82

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 28

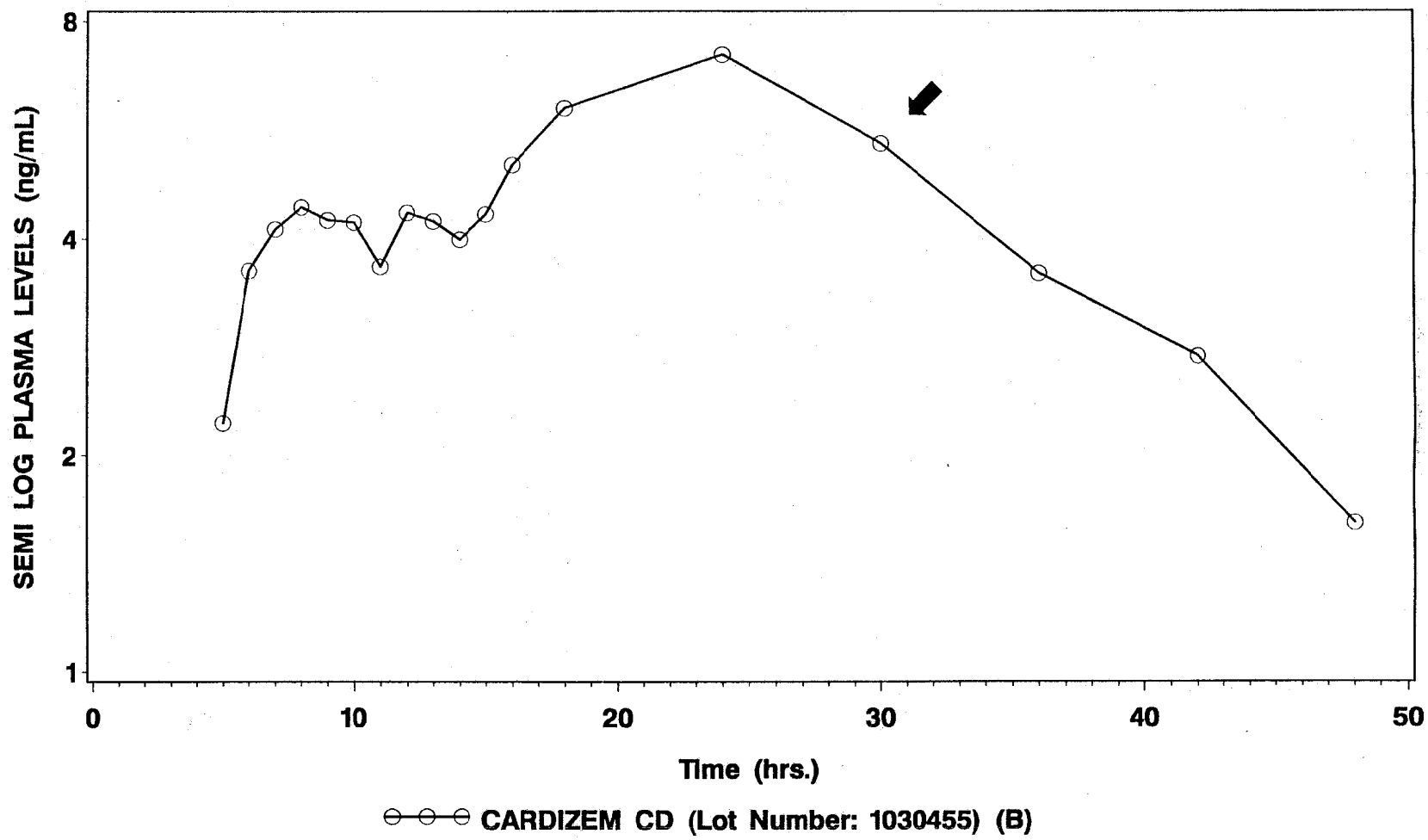


FIGURE 2.83

**Distribution of Difference of AUC (0-t) Between Formulations for DESACETYLDILTIAZEM
(STUDY # 2443)**

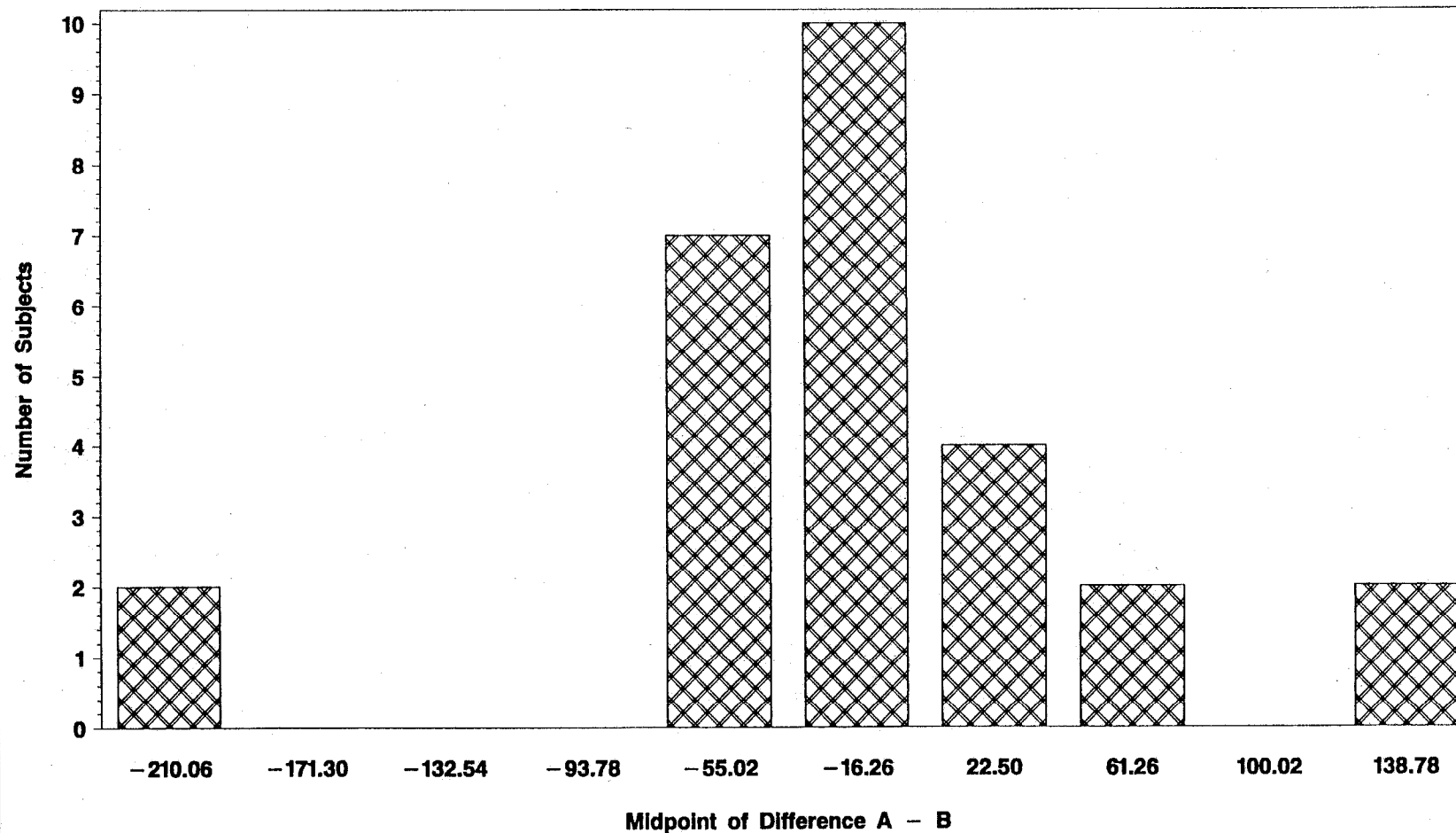


FIGURE 2.A

**Distribution of Ratio of AUC (0-t) Between Formulations for DESACETYLDILTIAZEM
(STUDY # 2443)**

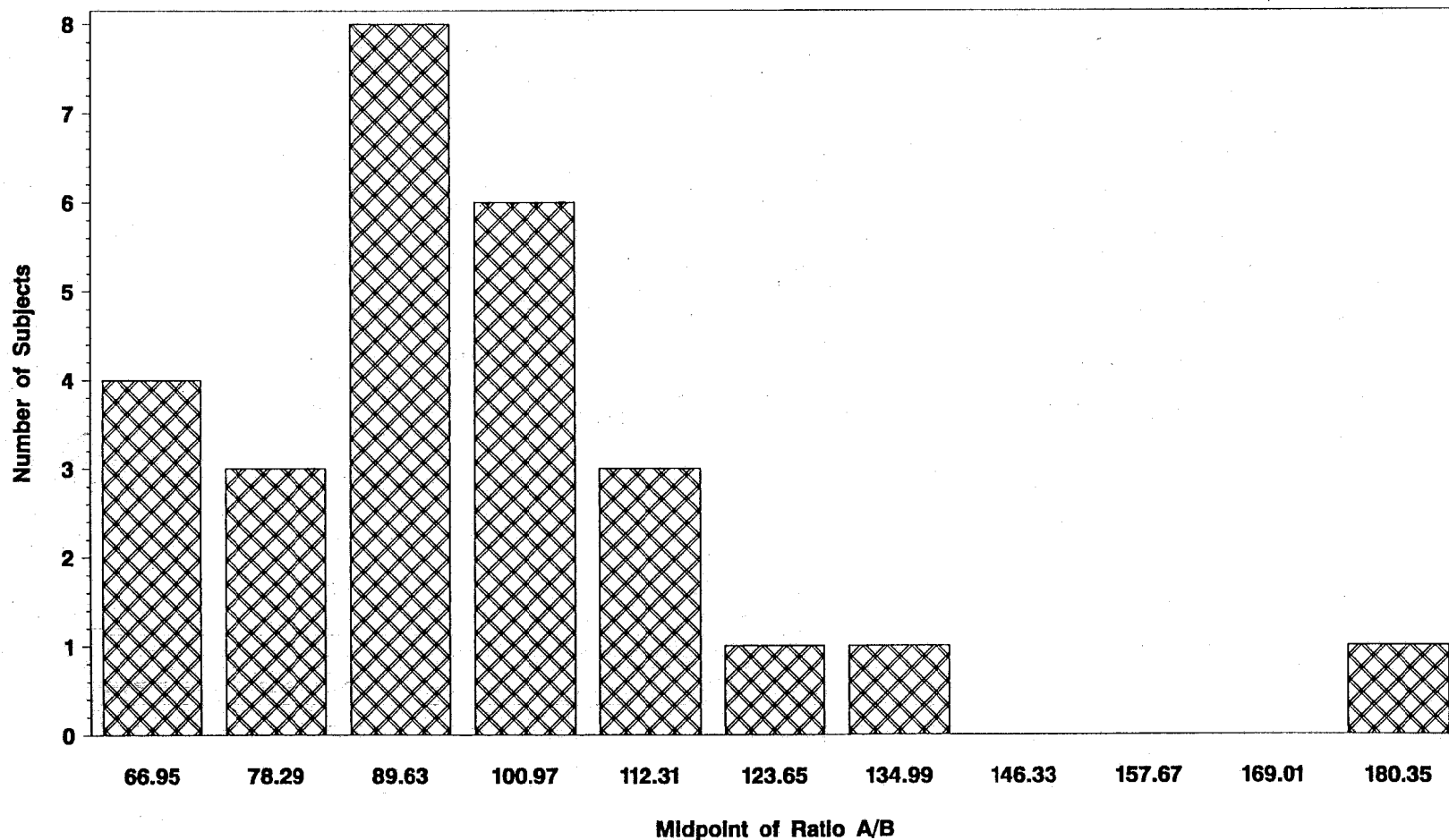


FIGURE 2.B

**Distribution of Difference of AUC (0–inf) Between Formulations for DESACETYLDILTIAZEM
(STUDY # 2443)**

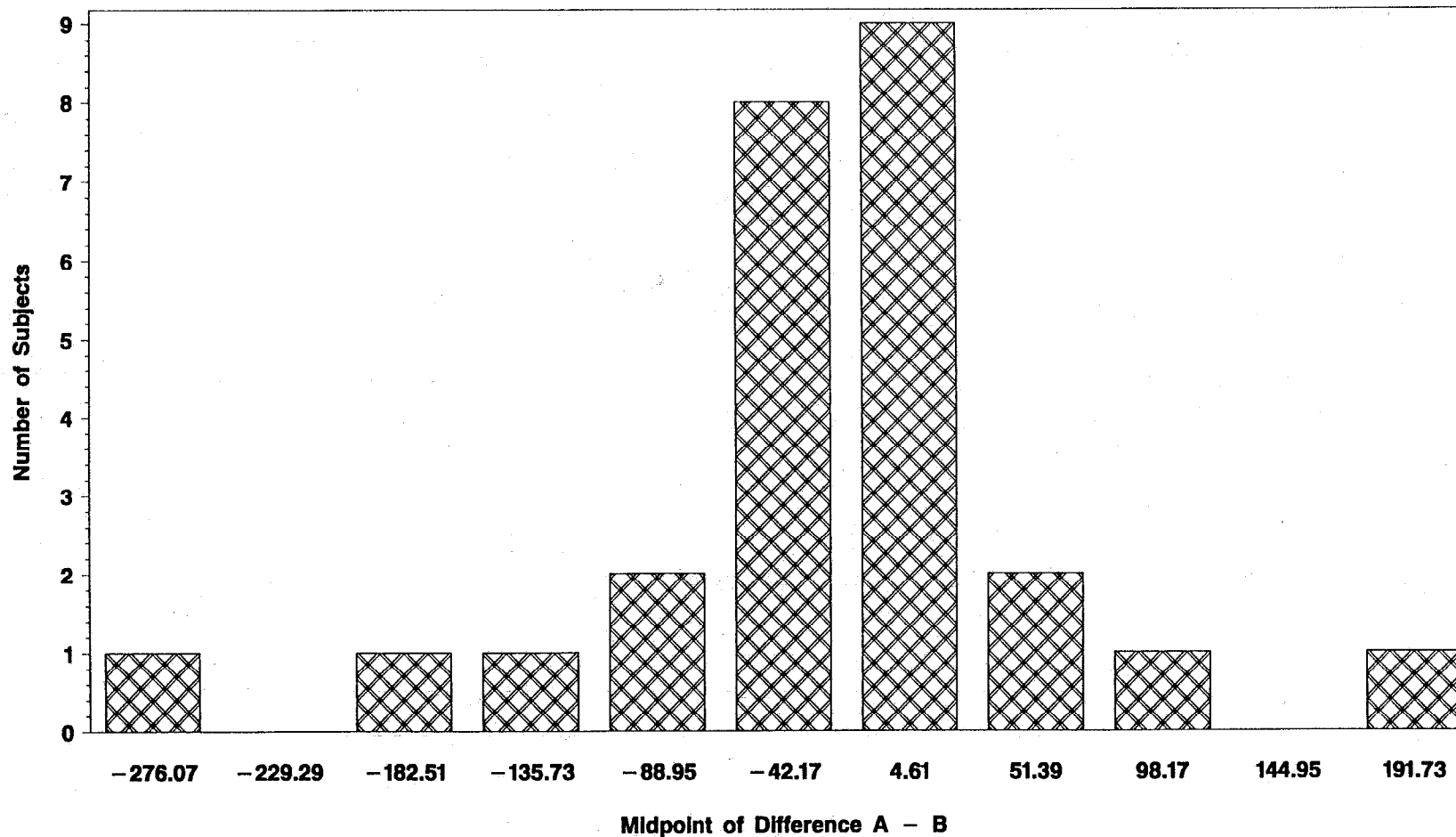


FIGURE 2.C

**Distribution of Ratio of AUC (0 – inf) Between Formulations for DESACETYLDILTIAZEM
(STUDY # 2443)**

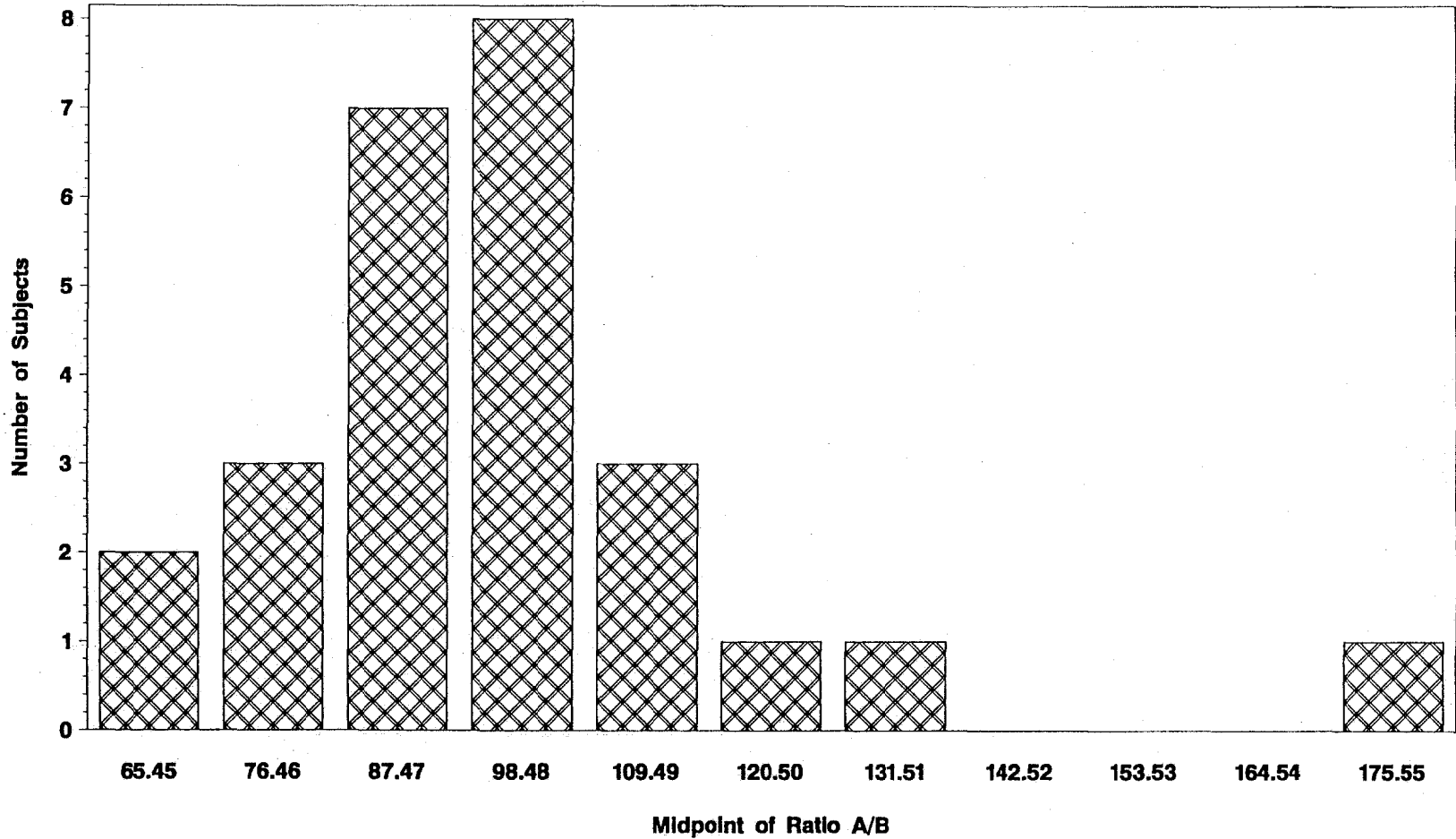


FIGURE 2.D

**Distribution of Difference of Cmax Between Formulations for DESACETYLDILTIAZEM
(STUDY # 2443)**

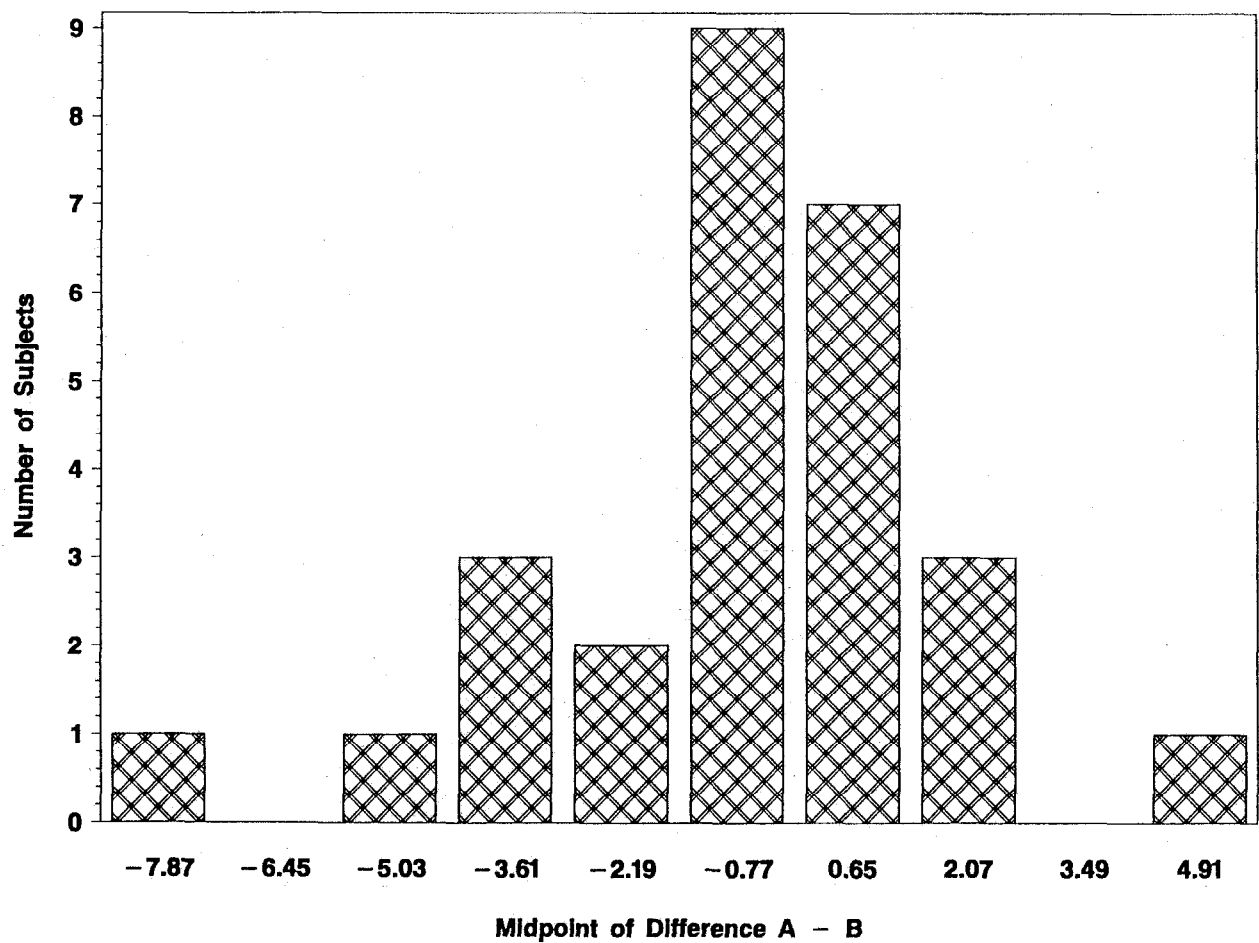


FIGURE 2.E

**Distribution of Ratio of Cmax Between Formulations for DESACETYLDILTIAZEM
(STUDY # 2443)**

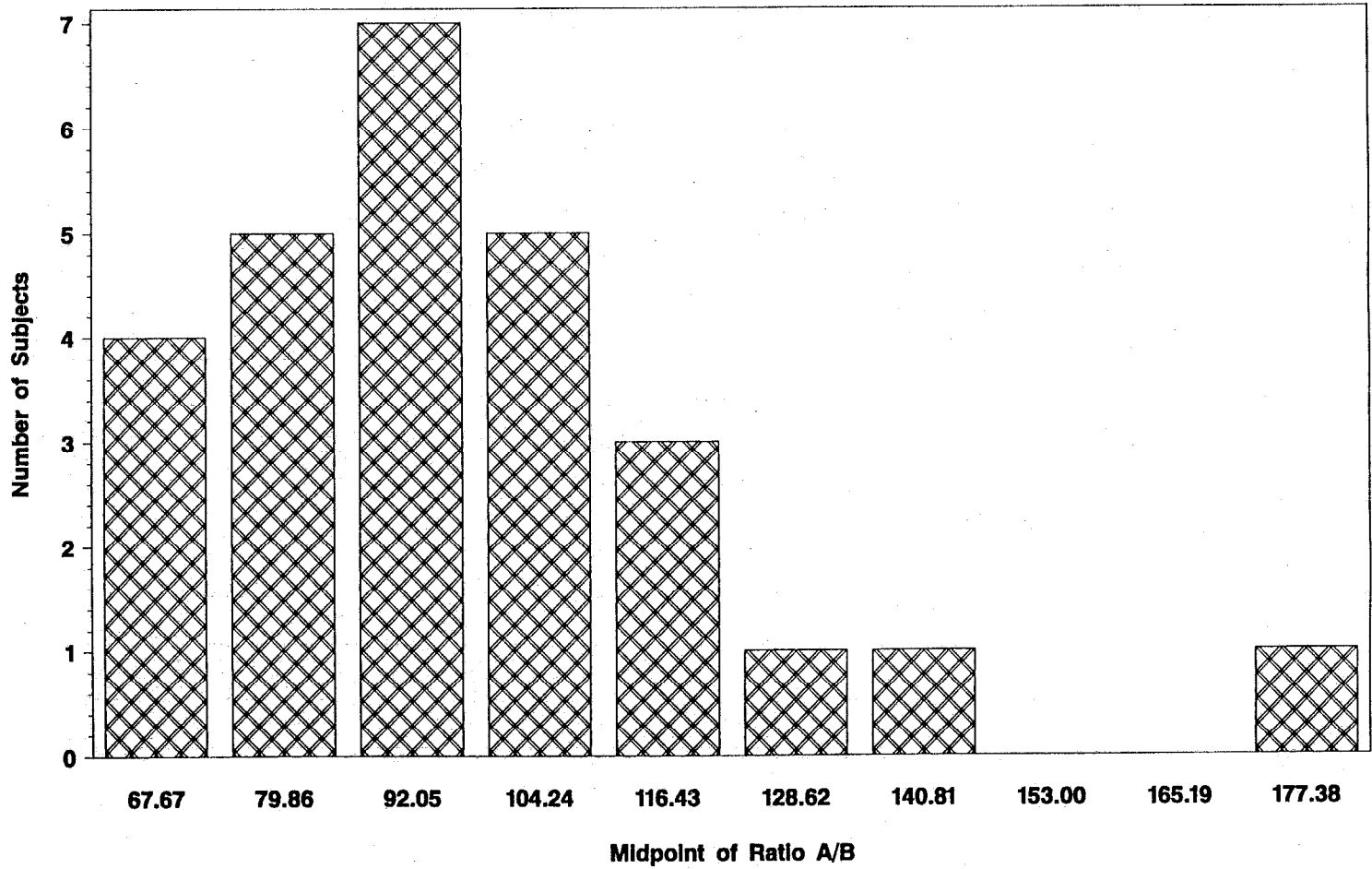


FIGURE 2.F

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS

STUDY # 2443: ALL SUBJECTS IN TEST GROUP

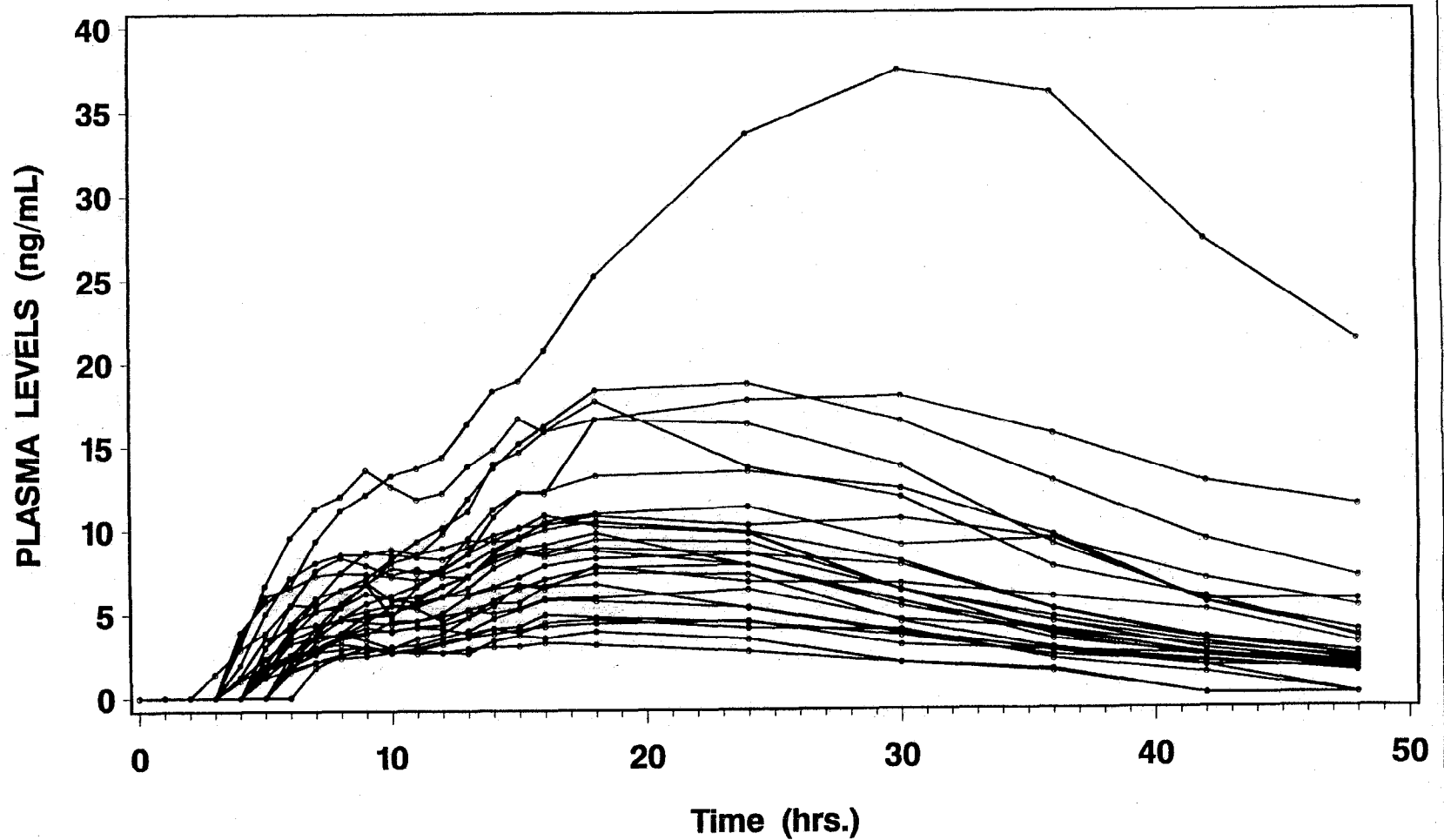


FIGURE 2.84

PLASMA DESACETYLDILTIAZEM CONCENTRATIONS
STUDY # 2443: ALL SUBJECTS IN REFERENCE GROUP

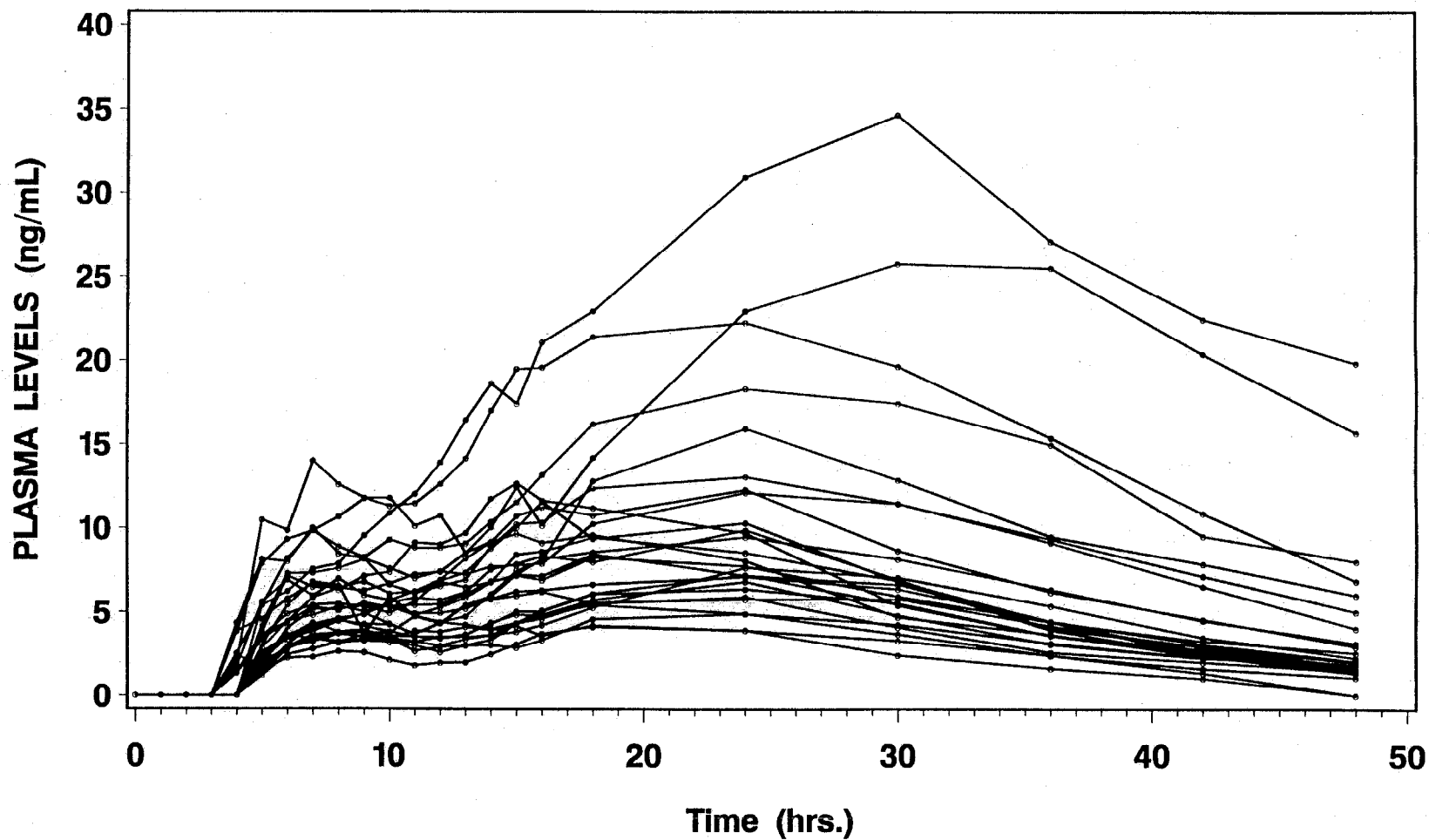


FIGURE 2.85

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS

STUDY # 2443: ALL SUBJECTS IN TEST GROUP

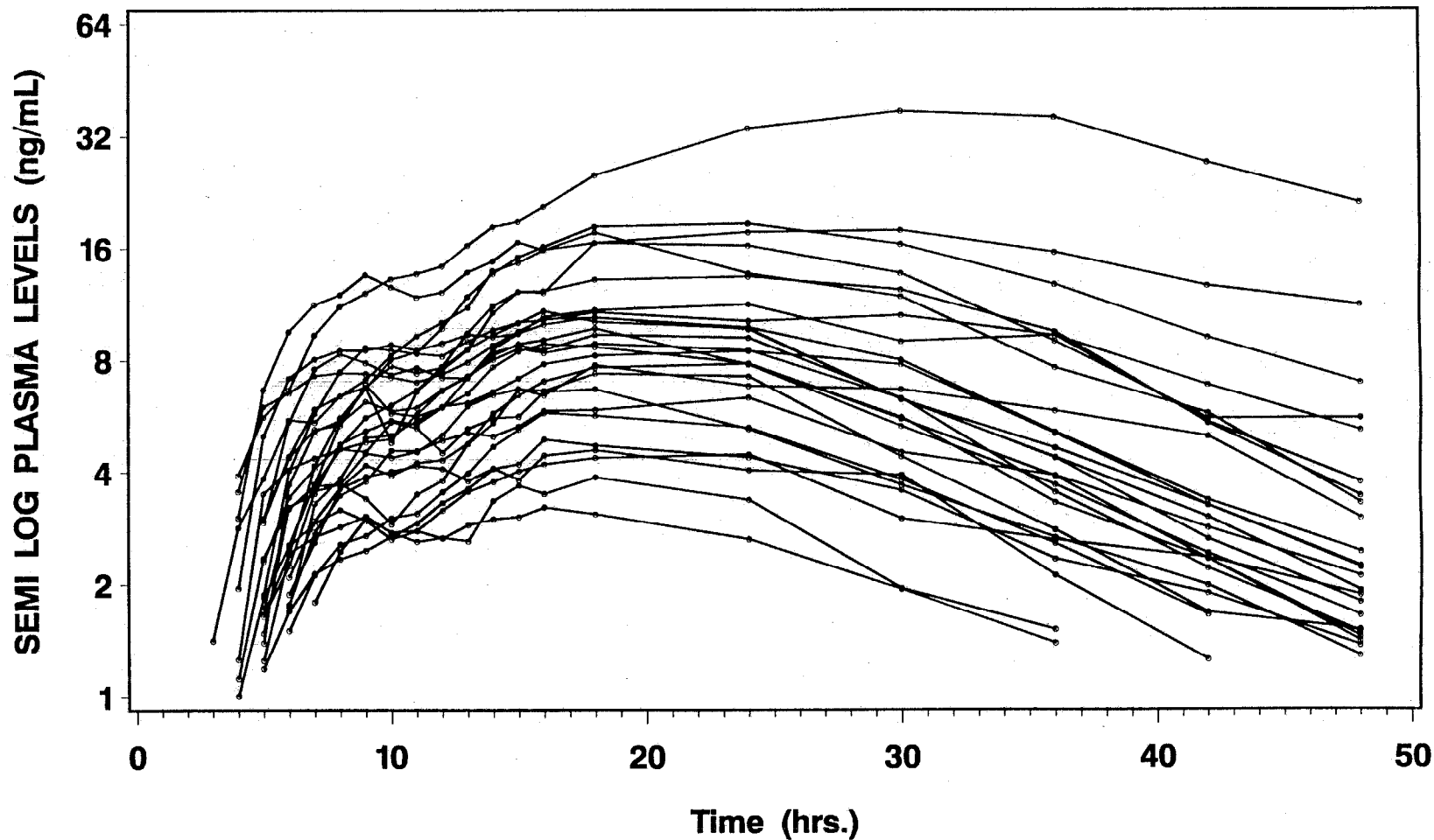


FIGURE 2.86

SEMI LOG PLASMA DESACETYLDILTIAZEM CONCENTRATIONS
STUDY # 2443: ALL SUBJECTS IN REFERENCE GROUP

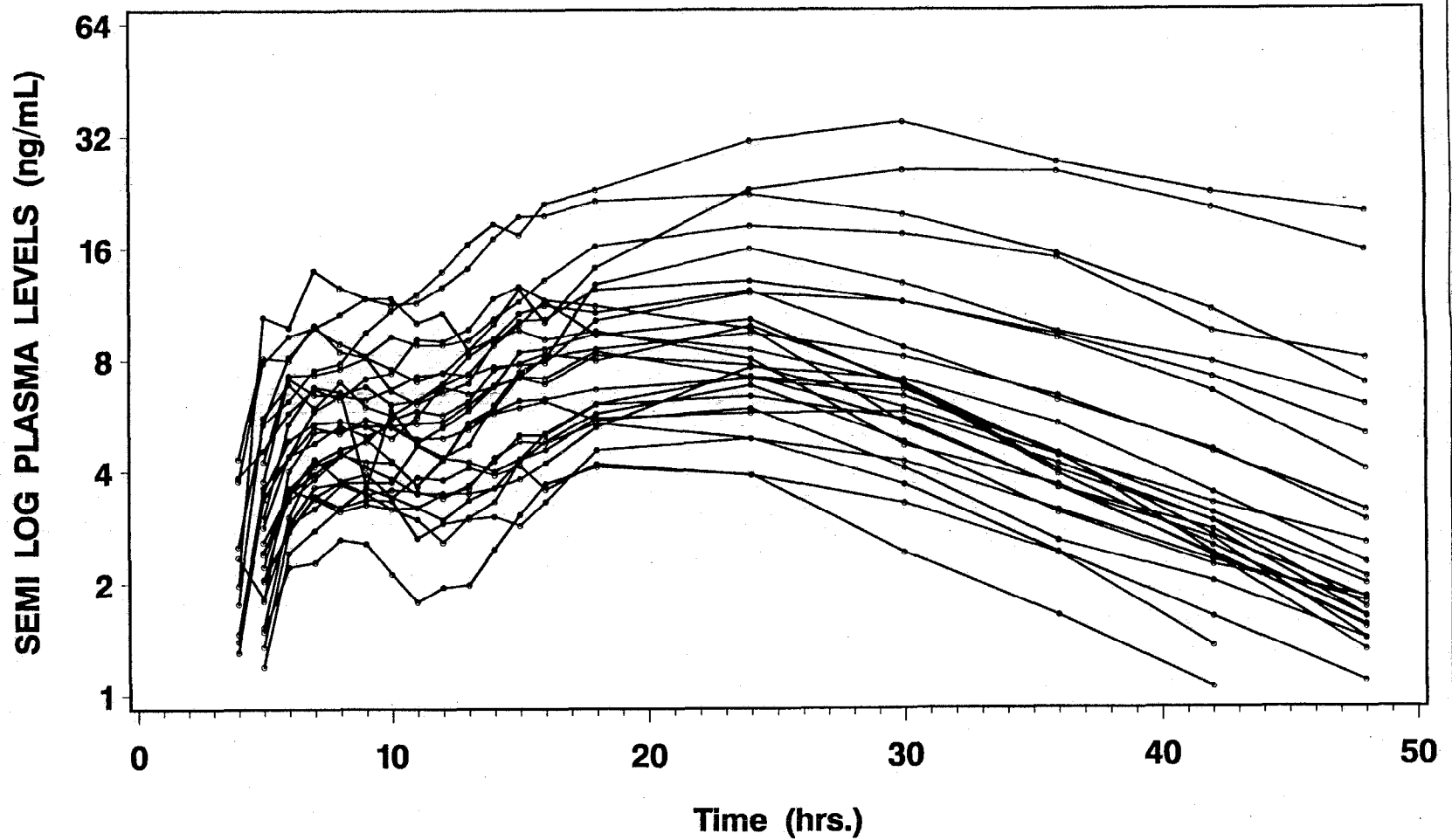


FIGURE 2.87

SECTION 3.0: PLASMA N-DESMETHYLDILTIAZEM

TABLES

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
Study # 2443 (B01-527PK-DILG12)
TABLE 3. 1.

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF ONE (1) CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg CAPSULE
(Andrx Pharmaceuticals, Inc. (A), Lot Number: 600A073, Expiry Date: 07/02)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION											
	0.00	1.00	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00	11.00
01	N.Q.	N.Q.	N.Q.	3.038	10.866	19.650	20.760	21.936	23.274	21.668	25.066	25.265
03	N.Q.	N.Q.	N.Q.**	N.Q.	3.236	11.487	21.362	25.739	28.527	28.447	31.176	31.599
04	N.Q.	N.Q.**	N.Q.	N.Q.	3.928	12.674	14.228	20.944	21.989	22.082	24.582	24.198
05	N.Q.	N.Q.	N.Q.	3.058	8.263	15.703	20.113	19.763	22.159	24.687	27.770	29.424
06	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	8.462	11.996	16.992	18.488	17.339	16.331	16.205
07	N.Q.	N.Q.	N.Q.	4.054	22.791	35.360	32.284	32.617	30.993	29.637	29.961	28.879
08	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	6.376	15.225	19.674	20.851	23.689	22.568	19.396
09	N.Q.	N.Q.	N.Q.	N.Q.	5.574	11.146	25.851	33.543	36.487	39.294	42.035	39.682
10	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	17.731	20.780	19.149	18.383	16.142	14.731	12.651
11	N.Q.	N.Q.	N.Q.	N.Q.	11.648	21.026	27.296	32.834	31.143	30.249	30.308	29.079
12	N.Q.	N.Q.	N.Q.	N.Q.	3.507	14.323	19.621	16.695	17.788	16.810	16.768	17.071
13	N.Q.	N.Q.	N.Q.	N.Q.	10.273	17.332	19.445	18.394	17.747	16.696	14.955	14.368
14	N.Q.	N.Q.	N.Q.	10.844	17.559	19.341	21.650	24.815	23.752	24.898	28.260	29.333
15	N.Q.	N.Q.	N.Q.	N.Q.	8.778	13.137	15.614	16.864	14.765	14.901	18.008	18.814
16	N.Q.	N.Q.	N.Q.	5.049	20.568	19.334	22.629	28.895	29.382	27.132	25.270	24.631**
17	N.Q.	N.Q.	N.Q.	N.Q.	8.921	19.479	25.929	26.890	28.829	28.398	28.257	27.043
18	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	6.622	15.067	23.683	24.851	24.080	25.827	24.037
19	N.Q.	N.Q.	N.Q.	N.Q.	14.125	28.815	29.783	34.246	37.790	38.867	39.247	37.907
20	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	10.815	19.276	21.100	22.861	25.494	28.394	26.472
21	N.Q.	N.Q.	N.Q.	N.Q.	10.834	20.448	25.163	24.531	23.380	20.594	18.691	19.013
22	N.Q.	N.Q.	N.Q.	3.408**	6.915	14.149	16.579	21.102	22.797	26.150	27.042	25.621
23	N.Q.	N.Q.	N.Q.	N.Q.	3.863	12.005	23.150	30.621	30.956	33.734	31.139	28.234
24	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	6.458	10.638	15.196	17.907	19.829	22.120	21.278
25	N.Q.	N.Q.	N.Q.	N.Q.	3.214	8.685	13.139	16.342	18.383	18.597	18.340	19.426
26	N.Q.	N.Q.	N.Q.	N.Q.	3.658	10.417	17.150	21.399	22.635	23.858	23.155	23.238
27	N.Q.	N.Q.	N.Q.	N.Q.	4.108	28.646	47.390	47.073	45.848	42.236	39.398	39.584
28	N.Q.	N.Q.	N.Q.	N.Q.	4.026	14.708	20.591	22.682	27.923	25.749	31.171	28.822
MEAN	0.000*	0.000*	0.000*	1.091*	6.913*	15.716	21.211	24.212	25.181	25.232	25.947	25.232
SD(±)	0.000*	0.000*	0.000*	2.462*	6.356*	7.129	7.465	7.285	7.178	7.162	7.308	7.071
C.V. (%)	0.000*	0.000*	0.000*	225.705*	91.938*	45.363	35.191	30.088	28.504	28.384	28.163	28.022
Range (Min.)	0.000*	0.000*	0.000*	0.000*	0.000*	6.376	10.638	15.196	14.765	14.901	14.731	12.651
(Max.)	0.000	0.000	0.000	10.844	22.791	35.360	47.390	47.073	45.848	42.236	42.035	39.682
N =	27	27	27	27	27	27	27	27	27	27	27	27

Limit of quantitation = 3.006 ng/mL

N.Q. = Not quantifiable N.D. = No Data N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.Q.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 1. (Continued)

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF ONE (1) CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg CAPSULE
 (Andrx Pharmaceuticals, Inc. (A), Lot Number: 600A073, Expiry Date: 07/02)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION										
	12.00	13.00	14.00	15.00	16.00	18.00	24.00	30.00	36.00	42.00	48.00
01	25.198	27.464	32.096	29.776	33.392	30.131	22.982	17.503	11.259	9.011	5.636
03	36.002	40.015	43.937**	47.910	49.049	54.533	54.104**	39.145	25.991	16.107	12.132
04	25.277**	29.673	37.127	35.878	40.318**	39.110	31.406	26.650	20.525**	15.357	11.568**
05	31.044	35.417	38.745	41.194	40.378	41.676	28.037	23.855	16.239	10.716	6.675
06	17.313	17.627	20.854	21.183	23.497	22.978	17.398	15.231	11.488	9.057	6.565
07	30.918	32.631	35.234	36.851	39.481	36.083	28.232	23.744	15.244	10.451	6.917
08	18.349	18.536	21.804	21.377	21.806	21.443	15.539	13.466	7.711	4.759	3.221
09	41.951	43.007	49.485	49.084	53.809	53.843	41.125	36.043	26.169	16.472	9.858
10	14.723	16.616	17.797	20.369	20.428	19.363	12.326	8.460	4.494	N.Q.	N.Q.
11	28.647	30.498	31.069	34.013	34.170	33.697	29.097	25.206	17.514	12.520	7.902
12	20.639	24.222	26.761	26.398	27.030	26.338	19.550	14.361	9.564	5.373	3.742
13	13.992	15.258	16.389	15.678	16.560	16.344	12.665	8.979	5.491	N.Q.	N.Q.
14	29.259	29.465	33.003	32.790	34.133	31.279	25.850	19.491	14.532	10.433	7.138
15	19.646	24.108	24.697	26.597	25.132	22.131	17.086	13.970	10.339	7.444	4.986
16	25.343	27.379	30.762	32.289	33.293	32.081	23.325	18.321	12.350	7.518	4.680
17	31.453	35.038	37.079	38.748	37.245	35.857	25.165	19.878	15.002	9.884	5.748
18	24.708	26.117	27.392	32.528	33.241	35.396	29.063	24.071	15.662	9.403	6.212**
19	37.298	37.067	39.840	43.997	43.215	42.322	36.588	35.149	34.019	20.015	14.094
20	29.606	31.456	35.475	36.601	38.243	43.239	29.620	21.857	12.765	7.444	5.209
21	22.373	26.308	27.512	32.272	31.763	29.104	22.208	14.217	8.768	5.243	3.388
22	25.620	28.964	30.400	29.993	29.902	32.275**	23.766	20.405	15.324	10.972	6.631
23	26.513	27.020	27.737	28.674	29.943	29.799	21.816	20.062	15.199	10.275	6.745
24	21.817	26.166	30.126	32.013	34.522	34.560	29.709	25.739	19.624	14.142	9.929
25	21.128	25.433	29.182	31.238	31.782	28.226	21.991	16.369	9.837	5.994	3.581
26	23.877	24.623	30.716	36.769	36.416	36.903	30.892	22.346	13.778	8.933	5.234
27	39.123	41.039	45.083	48.714	49.600	50.976	37.399	31.193	22.845	15.401	9.432
28	27.373	28.955**	26.345	29.610	30.909**	29.484	23.819	19.356	15.910	11.911	8.990
MEAN	26.266	28.522	31.357	33.057	34.047	33.673	26.324	21.299	15.098	9.809*	6.526*
SD (±)	7.075	7.107	7.978	8.490	8.817	9.782	9.008	7.688	6.623	4.705*	3.322*
C.V. (%)	26.935	24.918	25.442	25.684	25.897	29.051	34.221	36.094	43.869	47.969*	50.896*
Range (Min.)	13.992	15.258	16.389	15.678	16.560	16.344	12.326	8.460	4.494	0.000*	0.000*
(Max.)	41.951	43.007	49.485	49.084	53.809	54.533	54.104	39.145	34.019	20.015	14.094
N =	27	27	27	27	27	27	27	27	27	27	27

Limit of quantitation = 3.006 ng/mL

N.Q. = Not quantifiable

N.D. = No Data

N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.O.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
A DIVISION OF BIOVAIL CORPORATION
Study # 2443 (B01-527PK-DILG12)
TABLE 3. 2.

PLASMA N-DRSMETHYLDILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF 1 x 300 CARDIZEM[®] CD (DILTIAZEM HCl) CAPSULE
(Aventis Pharmaceuticals, Inc. (B), Lot Number: 1030455, Expiry Date: 11/2002)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION											
	0.00	1.00	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00	11.00
01	N.Q.	N.Q.	N.Q.	N.Q.	11.516	29.555	32.303	31.001	29.412	28.386	30.137	30.535
03	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	22.237	36.561	36.932	32.394	26.455	29.226	25.269
04	N.Q.	N.Q.	N.Q.	N.Q.	9.046	28.174	26.389	30.834	29.318	27.902	28.575	23.384
05	N.Q.	N.Q.	N.Q.	N.Q.	13.971	25.282	27.051	26.001	26.238	24.945	25.319	24.454
06	N.Q.	N.Q.	N.D.	N.Q.	3.539	22.803	22.943	21.746	19.421	16.438	15.800	13.493
07	N.Q.	N.Q.	N.Q.	N.Q.	13.148	25.544	28.833	27.249	25.686	26.058	24.774	24.513
08	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	19.500	26.182	28.382	25.341	22.936	21.286	17.881
09	N.Q.	N.Q.	N.Q.	10.696	53.732	43.801	46.884	47.136	48.807	47.377	55.750	53.538
10	N.Q.	N.Q.	N.Q.	N.Q.	5.082	16.892	17.053	15.139	15.308	13.341	11.820	9.542
11	N.Q.	N.Q.	N.Q.	N.Q.	15.767	22.135	25.958	25.937	26.528	27.819	30.203	29.141
12	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	12.188	22.572	22.425	20.789	18.040	16.669	15.002
13	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	10.420	16.486	17.667	17.654	17.444	17.180	17.482
14	N.Q.	N.Q.	N.Q.	N.Q.	4.879	14.292	15.707	19.469	23.289	21.498	22.986	22.500
15	N.Q.	N.Q.	N.Q.	N.Q.	18.847	15.908	23.249	22.564	22.583	22.394	24.671	27.645
16	N.Q.	N.Q.	N.Q.	3.588	22.516	29.585	27.046	27.179	26.376	29.583	30.884	32.691
17	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	16.304	22.810	23.326	24.243	23.459	22.638	22.140
18	N.Q.	N.Q.	N.Q.	N.Q.	6.394	27.795	26.421	26.369	24.623	21.242	20.314	17.775
19	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	20.709	25.041	27.928	26.978	26.108	26.128	23.615
20	N.Q.	N.Q.	N.Q.	N.Q.	N.Q.	11.874	19.469	24.593	25.948	24.354	27.442	27.331
21	N.Q.	N.Q.	N.Q.	N.Q.	7.271	17.589	33.115	29.579	26.726	24.438	20.546	18.162
22	N.Q.	N.Q.	N.Q.	N.Q.	3.365	23.165	26.472	28.753	29.182	29.011	27.912	23.593
23	N.Q.	N.Q.	N.Q.	N.Q.	25.051	36.609**	33.634	33.469	29.704	26.224	24.263	21.275
24	N.Q.	N.Q.	N.O.	N.O.	5.452	21.680	29.788	34.346	33.360	31.975	30.408	26.274
25	N.Q.	N.Q.	N.Q.	N.Q.	10.338	24.635	25.442	24.294	22.292	21.353	19.953	19.060
26	N.Q.	N.Q.	N.Q.	N.Q.	11.160	24.102	29.441	30.747	28.491	26.263	26.682	26.568
27	N.Q.	N.Q.	N.Q.	N.Q.	9.052	29.791	38.205	41.187	38.992	35.847	34.176	32.806
28	N.Q.	N.Q.	N.Q.	N.Q.	14.172	31.733	32.549	33.677	31.514	28.545	27.806	23.625
MEAN	0.000*	0.000*	0.000*	0.529*	9.789*	23.122	27.319	28.071	27.081	25.535	25.687	24.048
SD (±)	0.000*	0.000*	0.000*	2.146*	11.320*	7.718	6.899	6.945	6.593	6.543	8.019	8.144
C.V. (%)	0.000*	0.000*	0.000*	405.614*	115.647*	33.378	25.253	24.740	24.346	25.623	31.217	33.865
Range (Min.)	0.000*	0.000*	0.000*	0.000*	0.000*	10.420	15.707	15.139	15.308	13.341	11.820	9.542
(Max.)	0.000	0.000	0.000	10.696	53.732	43.801	46.884	47.136	48.807	47.377	55.750	53.538
N =	27	27	26	27	27	27	27	27	27	27	27	27

Limit of quantitation = 3.006 ng/mL

N.Q. = Not quantifiable

N.D. = No Data

N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.Q.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 2. (Continued)

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATION (ng/mL) FOLLOWING THE ADMINISTRATION OF 1 x 300 CARDIZEM[®] CD (DILTIAZEM HCl) CAPSULE
 (Aventis Pharmaceuticals, Inc. (B), Lot Number: 1030455, Expiry Date: 11/2002)

Subject No.	HOURS FOLLOWING DRUG ADMINISTRATION										
	12.00	13.00	14.00	15.00	16.00	18.00	24.00	30.00	36.00	42.00	48.00
01	30.404	38.321	42.107	39.684	36.710	35.932	23.961	18.639	12.485	8.583	4.454**
03	23.391	27.780	32.482	43.286	50.379	57.854	54.777	52.377	33.450	21.513	15.065
04	24.435	23.587**	27.200	31.135**	33.690**	36.591	39.086	32.715	28.531	20.461**	14.575**
05	27.548	29.049	33.041	35.242	37.644	37.583	35.472	33.093	22.705	14.633	9.565
06	14.459	14.362	14.972	15.899	18.816	20.936	22.994	18.175	12.804	7.976	5.313
07	27.554	29.209	32.471	33.018	31.678	32.409	25.099	20.280	13.938	9.207	5.533
08	16.816	17.004	19.438	23.084	25.747	27.543	21.250	19.185	12.097	8.728	5.621
09	54.198	57.488	61.745	62.086	64.121	62.485	44.060	33.558	22.293	15.331	9.241
10	9.648	12.867	17.350	20.820	20.963	21.373	13.412	9.161	5.418	3.262	N.Q.
11	31.315	34.975	40.383	45.248	43.726	47.602	44.281	37.375	29.128	22.095	13.979
12	14.475	14.974	16.803	18.020	18.596	18.154	13.768	11.060	6.799	4.493	N.Q.
13	17.433	17.369	18.877	19.672	20.170	19.469	15.293	12.387	9.023	4.983	N.Q.
14	28.848	31.240	34.097	35.021	36.299	34.942	30.055	24.919	17.953	13.687	9.607
15	28.090	30.241	28.019	27.999	27.734	24.481	19.879	15.952**	9.636	7.863	5.842
16	34.052	37.756	38.883	36.098	38.715	37.172	29.579	22.166	12.463	7.858	5.819
17	21.591	23.763	27.778	29.090	29.856	30.118	22.949	22.275**	14.887	11.140	6.329
18	16.853	17.277	18.874	21.295	25.173	25.909	26.216	25.162	16.865	10.704	6.448
19	25.921	31.315	34.827	40.246	44.524	50.407	45.109	40.139	31.072	22.739	14.149
20	26.556	33.138	34.334	34.584	35.310	31.428	31.286	22.785	14.433	8.920	5.181
21	16.307	18.754	24.695	26.334	28.502	29.800	23.420	16.359	11.171	6.479	5.453
22	25.759	29.532	32.278	35.817	38.932	41.621	30.880	27.796	20.151	13.489	9.254
23	21.414	21.436	21.449	23.098	23.549	25.928	23.992	21.301	16.297	11.495	7.876
24	25.346	26.973	27.727	30.965	34.077	40.783	35.325	31.954	22.723	15.983	11.995
25	20.722	23.504	26.887	30.277	30.845	28.588	21.050	15.898	10.614	5.997	3.946
26	29.826	33.429	38.867	45.862	53.956	38.757	35.399	24.694	15.683	9.311	5.798
27	33.901**	37.111	36.466	42.443	41.608**	45.886	38.454	30.735	21.545	16.166	11.780
28	23.637	24.650	26.454	27.141	30.286	36.365	30.954	24.305	17.100	12.514	8.321
MEAN	24.833	27.300	29.945	32.351	34.134	34.819	29.556	24.609	17.084	11.689	7.450*
SD(±)	8.589	9.626	10.022	10.343	10.939	11.182	10.285	9.680	7.363	5.484	4.256*
C.V.(%)	34.586	35.260	33.468	31.973	32.046	32.113	34.800	39.337	43.097	46.911	57.127*
Range (Min.)	9.648	12.867	14.972	15.899	18.596	18.154	13.412	9.161	5.418	3.262	0.000*
(Max.)	54.198	57.488	61.745	62.086	64.121	62.485	54.777	52.377	33.450	22.739	15.065
N =	27	27	27	27	27	27	27	27	27	27	27

Limit of quantitation = 3.006 ng/mL

N.Q. = Not quantifiable N.D. = No Data N.A. = Not Applicable

* Mean, SD, CV and Range are calculated using a value of 0.00 ng/mL for N.Q.

** Actual sampling time was used for pharmacokinetic and statistical analysis to account for the deviation in sampling time.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 3.

SUMMARY OF N-DESMETHYLDILTIAZEM PARAMETERS FOR EACH SUBJECT GIVEN THE ONE (1) CARTIA XT™ (DILTIAZEM HCl EXTENDED RELEASE CAPSULES, USP) 300 mg CAPSULE
 (Andrx Pharmaceuticals, Inc. (A), Lot Number: 600A073, Expiry Date: 07/02)

SUBJECT	SEQ	PERIOD	C _{max} (ng/mL)	T _{max} (hrs)	AUC(0-t) (ng.hr/mL)	AUC(0-inf) (ng.hr/mL)	AUC(0-t)		K _{el} (hr ⁻¹)	T _{half} (hrs)
							----- (%) AUC(0-inf)			
01	AB	1	33.39	16.00	838.11	939.86	89.17	0.055	12.51	
03	AB	1	54.53	18.00	1489.68	1677.27	88.82	0.065	10.72	
04	BA	2	40.32	16.03	1088.05	1336.63	81.40	0.047	14.90	
05	BA	2	41.68	18.00	1037.72	1132.25	91.65	0.071	9.82	
06	BA	2	23.50	16.00	648.69	791.27	81.98	0.046	15.05	
07	BA	2	39.48	16.00	1072.54	1174.32	91.33	0.068	10.20	
08	AB	1	23.69	9.00	584.84	625.32	93.53	0.080	8.71	
09	BA	2	53.84	18.00	1461.65	1597.56	91.49	0.073	9.56	
10	AB	1	20.78	6.00	435.36	492.03	88.48	0.079	8.74	
11	AB	1	34.17	16.00	1053.58	1177.84	89.45	0.064	10.90	
12	AB	1	27.03	16.00	670.81	719.50	93.23	0.077	9.02	
13	BA	2	19.45	6.00	427.08	518.19	82.42	0.060	11.50	
14	AB	1	34.13	16.00	944.53	1072.57	88.06	0.056	12.43	
15	AB	1	26.60	15.00	650.14	737.63	88.14	0.057	12.16	
16	BA	2	33.29	16.00	880.05	941.22	93.50	0.077	9.06	
17	AB	1	38.75	15.00	972.18	1055.49	92.11	0.069	10.05	
18	AB	1	35.40	18.00	934.32	1015.88	91.97	0.076	9.10	
19	BA	2	44.00	15.00	1450.00	1708.45	84.87	0.055	12.71	
20	AB	1	43.24	18.00	963.61	1028.17	93.72	0.081	8.59	
21	AB	1	32.27	15.00	747.96	790.68	94.60	0.079	8.74	
22	AB	1	32.28	18.02	895.21	1002.56	89.29	0.062	11.22	
23	BA	2	33.73	9.00	892.10	1002.63	88.98	0.061	11.36	
24	BA	2	34.56	18.00	978.64	1165.67	83.96	0.053	13.06	
25	BA	2	31.78	16.00	719.57	762.08	94.42	0.084	8.23	
26	BA	2	36.90	18.00	935.13	1000.72	93.45	0.080	8.69	
27	BA	2	50.98	18.00	1415.87	1557.97	90.88	0.066	10.44	
28	BA	2	31.17	10.00	905.21	1135.06	79.75	0.039	17.72	
MEAN			35.22	15.04	929.36	1042.92	89.28	0.07	10.93	
SD (±)			9.07	3.66	285.08	325.60	4.30	0.01	2.33	
C.V. (%)			25.74	24.37	30.68	31.22	4.82	18.52	21.30	
Range (Min.)			19.45	6.00	427.08	492.03	79.75	0.04	8.23	
(Max.)			54.53	18.02	1489.68	1708.45	94.60	0.08	17.72	
Num of subjects			27	27	27	27	27	27	27	

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 4.

SUMMARY OF N-DESMETHYLDILTIAZEM PARAMETERS FOR EACH SUBJECT GIVEN THE CARDIZEM® CD (DILTIAZEM HCl) CAPSULE
 (Aventis Pharmaceuticals, Inc. (B), Lot Number: 1030455, Expiry Date: 11/2002)

SUBJECT	SEQ	PERIOD	C _{max} (ng/mL)	T _{max} (hrs)	AUC(0-t) (ng.hr/mL)	AUC(0-inf) (ng.hr/mL)	AUC(0-t) ----- (%) AUC(0-inf)	K _{el} (hr ⁻¹)	T _{1/2t} (hrs)
01	AB	2	42.11	14.00	967.63	1024.91	94.41	0.078	8.91
03	AB	2	57.85	18.00	1660.89	1877.16	88.48	0.070	9.95
04	BA	1	39.09	24.00	1275.46	1592.87	80.07	0.046	15.10
05	BA	1	37.64	16.00	1189.05	1326.91	89.61	0.069	9.99
06	BA	1	22.99	24.00	695.48	772.05	90.08	0.069	9.99
07	BA	1	33.02	15.00	922.95	999.95	92.30	0.072	9.65
08	AB	2	28.38	7.00	771.07	855.19	90.16	0.067	10.37
09	BA	1	64.12	16.00	1708.53	1839.20	92.90	0.071	9.80
10	AB	2	21.37	18.00	459.53	500.59	91.80	0.079	8.72
11	AB	2	47.60	18.00	1450.62	1710.56	84.80	0.054	12.89
12	AB	2	22.57	6.00	495.71	565.80	87.61	0.064	10.81
13	BA	1	20.17	16.00	530.98	622.89	85.25	0.054	12.78
14	AB	2	36.30	16.00	1016.55	1200.66	84.67	0.052	13.28
15	AB	2	30.24	13.00	769.33	886.72	86.76	0.050	13.93
16	BA	1	38.88	14.00	1032.85	1114.26	92.69	0.071	9.70
17	AB	2	30.12	18.00	868.96	962.30	90.30	0.068	10.22
18	AB	2	27.80	5.00	879.65	964.88	91.17	0.076	9.16
19	BA	1	50.41	18.00	1454.03	1700.79	85.49	0.057	12.09
20	AB	2	35.31	16.00	948.39	1011.51	93.76	0.082	8.45
21	AB	2	33.12	6.00	786.40	876.37	89.73	0.061	11.44
22	AB	2	41.62	18.00	1121.38	1271.41	88.20	0.062	11.24
23	BA	1	36.61	5.02	918.73	1060.47	86.63	0.056	12.47
24	BA	1	40.78	18.00	1210.44	1429.11	84.70	0.055	12.64
25	BA	1	30.85	16.00	762.57	812.40	93.87	0.079	8.75
26	BA	1	53.96	16.00	1115.32	1186.77	93.98	0.081	8.54
27	BA	1	45.89	18.00	1332.58	1555.95	85.64	0.053	13.14
28	BA	1	36.37	18.00	1050.59	1192.11	88.13	0.059	11.79
MEAN			37.23	15.07	1014.65	1144.95	89.01	0.06	10.96
SD (±)			11.01	5.12	325.54	381.10	3.64	0.01	1.84
C.V. (%)			29.59	33.96	32.08	33.29	4.09	16.27	16.83
Range (Min.)			20.17	5.00	459.53	500.59	80.07	0.05	8.45
(Max.)			64.12	24.00	1708.53	1877.16	94.41	0.08	15.10
Num of subjects			27	27	27	27	27	27	27

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 5.

AREA UNDER THE PLASMA DESMETHYLDILTIAZEM CONCENTRATION-TIME CURVES (0-t hrs.)

AUC (0-t) (ng.hr/mL)

SUBJECT No.	RAW SCALE			RATIO% #	LOG SCALE		
	CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg	DIFF		CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg	DIFF *
01	838.11	967.63	-129.53	86.61	6.7311	6.8749	-0.1437
03	1489.68	1660.89	-171.21	89.69	7.3063	7.4151	-0.1088
04	1088.05	1275.46	-187.41	85.31	6.9921	7.1511	-0.1589
05	1037.72	1189.05	-151.33	87.27	6.9448	7.0809	-0.1361
06	648.69	695.48	-46.79	93.27	6.4749	6.5446	-0.0696
07	1072.54	922.95	149.59	116.21	6.9778	6.8276	0.1502
08	584.84	771.07	-186.23	75.85	6.3713	6.6478	-0.2764
09	1461.65	1708.53	-246.88	85.55	7.2873	7.4434	-0.1561
10	435.36	459.53	-24.17	94.74	6.0762	6.1302	-0.0540
11	1053.58	1450.62	-397.04	72.63	6.9600	7.2797	-0.3198
12	670.81	495.71	175.11	135.32	6.5085	6.2060	0.3025
13	427.08	530.98	-103.90	80.43	6.0570	6.2747	-0.2178
14	944.53	1016.55	-72.01	92.92	6.8507	6.9242	-0.0735
15	650.14	769.33	-119.18	84.51	6.4772	6.6455	-0.1683
16	880.05	1032.85	-152.80	85.21	6.7800	6.9401	-0.1601
17	972.18	868.96	103.22	111.88	6.8795	6.7673	0.1122
18	934.32	879.65	54.66	106.21	6.8398	6.7795	0.0603
19	1450.00	1454.03	-4.03	99.72	7.2793	7.2821	-0.0028
20	963.61	948.39	15.23	101.61	6.8707	6.8548	0.0159
21	747.96	786.40	-38.44	95.11	6.6173	6.6675	-0.0501
22	895.21	1121.38	-226.17	79.83	6.7971	7.0223	-0.2253
23	892.10	918.73	-26.62	97.10	6.7936	6.8230	-0.0294
24	978.64	1210.44	-231.79	80.85	6.8862	7.0987	-0.2126
25	719.57	762.57	-43.00	94.36	6.5787	6.6367	-0.0580
26	935.13	1115.32	-180.19	83.84	6.8407	7.0169	-0.1762
27	1415.87	1332.58	83.29	106.25	7.2555	7.1949	0.0606
28	905.21	1050.59	-145.38	86.16	6.8082	6.9571	-0.1489
MEAN	929.36	1014.65	-85.30	92.91	6.7867	6.8699	-0.0831
SD(±)	285.08	325.54	132.09	13.63	0.3227	0.3381	0.1383
C.V.(%)	30.68	32.08	154.86	14.67	4.7554	4.9213	166.3690
Range (Min.)	427.08	459.53	-397.04	72.63	6.0570	6.1302	-0.3198
(Max.)	1489.68	1708.53	175.11	135.32	7.3063	7.4434	0.3025
Num of subjects	27	27	27	27	27	27	27
Geometric Mean					885.9850	962.8523	

RATIO% = (CARTIA XTTM / CARDIZEM[®] CD) × 100

* DIFF(Log Scale) = ln(CARTIA XTTM) - ln(CARDIZEM[®] CD)

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 6.

ANOVA ON DESMETHYLDILTIAZEM LOG AUC (0 - t hrs.)

The GLM Procedure

Dependent Variable: lauct

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	5.52633112	0.19736897	19.98	<.0001
Error	25	0.24698986	0.00987959		
Corrected Total	53	5.77332097			

R-Square	Coeff Var	Root MSE	lauct Mean
0.957219	1.455650	0.099396	6.828300

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.30727644	0.30727644	31.10	<.0001
subj(sq)	25	5.12403675	0.20496147	20.75	<.0001
peri	1	0.00170957	0.00170957	0.17	0.6810
drug	1	0.09224779	0.09224779	9.34	0.0053

The GLM Procedure
 Least Squares Means

drug	lauct LSMEAN	Standard Error	Pr > t
A	6.78414471	0.01914193	<.0001
B	6.86686445	0.01914193	<.0001

sq	lauct LSMEAN	Standard Error	Pr > t
AB	6.75001868	0.01949319	<.0001
BA	6.90099048	0.01878411	<.0001

peri	lauct LSMEAN	Standard Error	Pr > t
1	6.83113506	0.01914193	<.0001
2	6.81987410	0.01914193	<.0001

The GLM Procedure

Dependent Variable: lauct

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.30727644	0.30727644	1.50	0.2322

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	-0.08271974	0.02707078	-3.06	0.0053

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 7.

90% GEOMETRIC CONFIDENCE INTERVAL BASED ON AREA UNDER THE PLASMA DESMETHYLDILTIAZEM
 CONCENTRATION-TIME CURVES

LOG AUC (0-t) (ng.hr/mL)

Source	DF	TYPE III SS	Mean Square	F Value	Pr > F
ERROR	25	0.246990	0.009880	.	.
sq	1	0.307276	0.307276	31.102132	0.000008
subj(sq)	25	5.124037	0.204961	20.745940	0.000000
peri	1	0.001710	0.001710	0.173041	0.680973
drug	1	0.092248	0.092248	9.337204	0.005280

INTRA-SUBJECT C.V. = $100 \times \text{SQRT}(\text{MSE}) = 100 \times \text{SQRT}(0.009880) = 9.94 \%$

DIFFERENCE = TEST - REFERENCE = $6.784145 - 6.866864 = -.082720$

SE DIFFERENCE = 0.027071

AUC(0-t) RATIO = $100 \times e^{\frac{(\text{difference})}{\text{SE DIFFERENCE}}} = 100 \times e^{\frac{(6.784145 - 6.866864)}{0.027071}} = 92.06 \%$

90% GEOMETRIC CONFIDENCE INTERVAL

LOWER, UPPER = $100 \times e^{(\text{difference} \pm t_{0.05, 25} \times \text{SE difference})}$

LOWER = $100 \times e^{(-.082720 - 1.7081 \times 0.027071)} = 87.90 \%$

UPPER = $100 \times e^{(-.082720 + 1.7081 \times 0.027071)} = 96.42 \%$

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILGL2)
 TABLE 3. 8.

AREA UNDER THE PLASMA DESMETHYLDILTIAZEM CONCENTRATION-TIME CURVES (0 - infinity)

SUBJECT No.	RAW SCALE			RATIO% #	LOG SCALE		
	CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg	DIFF		CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg	DIFF *
01	939.86	1024.91	-85.05	91.70	6.8457	6.9324	-0.0866
03	1677.27	1877.16	-199.88	89.35	7.4249	7.5375	-0.1126
04	1336.63	1592.87	-256.24	83.91	7.1979	7.3733	-0.1754
05	1132.25	1326.91	-194.66	85.33	7.0320	7.1906	-0.1586
06	791.27	772.05	19.22	102.49	6.6736	6.6491	0.0246
07	1174.32	999.95	174.37	117.44	7.0684	6.9077	0.1607
08	625.32	855.19	-229.86	73.12	6.4383	6.7513	-0.3131
09	1597.56	1839.20	-241.65	86.86	7.3762	7.5171	-0.1409
10	492.03	500.59	-8.56	98.29	6.1985	6.2158	-0.0172
11	1177.84	1710.56	-532.72	68.86	7.0714	7.4446	-0.3731
12	719.50	565.80	153.70	127.17	6.5786	6.3382	0.2403
13	518.19	622.89	-104.70	83.19	6.2503	6.4344	-0.1840
14	1072.57	1200.66	-128.09	89.33	6.9778	7.0906	-0.1128
15	737.63	886.72	-149.08	83.19	6.6034	6.7875	-0.1841
16	941.22	1114.26	-173.04	84.47	6.8472	7.0159	-0.1688
17	1055.49	962.30	93.19	109.68	6.9618	6.8693	0.0924
18	1015.88	964.88	51.00	105.29	6.9235	6.8720	0.0515
19	1708.45	1700.79	7.66	100.45	7.4433	7.4388	0.0045
20	1028.17	1011.51	16.65	101.65	6.9355	6.9192	0.0163
21	790.68	876.37	-85.69	90.22	6.6729	6.7758	-0.1029
22	1002.56	1271.41	-268.85	78.85	6.9103	7.1479	-0.2376
23	1002.63	1060.47	-57.84	94.55	6.9104	6.9665	-0.0561
24	1165.67	1429.11	-263.43	81.57	7.0611	7.2648	-0.2038
25	762.08	812.40	-50.32	93.81	6.6361	6.7000	-0.0639
26	1000.72	1186.77	-186.05	84.32	6.9085	7.0790	-0.1705
27	1557.97	1555.95	2.02	100.13	7.3511	7.3498	0.0013
28	1135.06	1192.11	-57.05	95.21	7.0344	7.0835	-0.0490
MEAN	1042.92	1144.95	-102.03	92.61	6.9012	6.9871	-0.0859
SD(±)	325.60	381.10	152.30	12.95	0.3233	0.3481	0.1367
C.V.(%)	31.22	33.29	149.26	13.99	4.6848	4.9826	159.1844
Range(Min.)	492.03	500.59	-532.72	68.86	6.1985	6.2158	-0.3731
(Max.)	1708.45	1877.16	174.37	127.17	7.4433	7.5375	0.2403
Num of subjects	27	27	27	27	27	27	27
Geometric Mean					993.4662	1082.5774	

RATIO% = (CARTIA XT™ / CARDIZEM® CD) × 100
 * DIFF(Log Scale) = ln(CARTIA XT™) - ln(CARDIZEM® CD)
 N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 9.

ANOVA ON DESMETHYLDILTIAZEM LOG AUC (0 - inf)

The GLM Procedure

Dependent Variable: lauci

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	5.72561811	0.20448636	21.03	<.0001
Error	25	0.24303388	0.00972136		
Corrected Total	53	5.96865200			

R-Square	Coeff Var	Root MSE	lauci Mean
0.959282	1.419849	0.098597	6.944184

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.40058982	0.40058982	41.21	<.0001
subj(sq)	25	5.22537512	0.20901500	21.50	<.0001
peri	1	0.00003826	0.00003826	0.00	0.9505
drug	1	0.09962282	0.09962282	10.25	0.0037

The GLM Procedure
 Least Squares Means

drug	lauci LSMEAN	Standard Error	Pr > t
A	6.89801063	0.01898802	<.0001
B	6.98397344	0.01898802	<.0001

sq	lauci LSMEAN	Standard Error	Pr > t
AB	6.85480317	0.01933645	<.0001
BA	7.02718090	0.01863307	<.0001

peri	lauci LSMEAN	Standard Error	Pr > t
1	6.94014976	0.01898802	<.0001
2	6.94183431	0.01898802	<.0001

The GLM Procedure

Dependent Variable: lauci

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.40058982	0.40058982	1.92	0.1785

Parameter	Estimate	Standard Error	t value	Pr > t
TEST - REF	-0.08596281	0.02685311	-3.20	0.0037

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 10.

90% GEOMETRIC CONFIDENCE INTERVAL BASED ON AREA UNDER THE PLASMA DESMETHYLDILTIAZEM
 CONCENTRATION-TIME CURVES

LOG AUC (0-inf) (ng.hr/mL)

Source	DF	TYPE III SS	Mean Square	F Value	Pr > F
ERROR	25	0.243034	0.009721	.	.
sq	1	0.400590	0.400590	41.207199	0.000001
subj(sq)	25	5.225375	0.209015	21.500603	0.000000
peri	1	0.000038	0.000038	0.003935	0.950479
drug	1	0.099623	0.099623	10.247833	0.003705

INTRA-SUBJECT C.V. = $100 \times \text{SQRT}(\text{MSE}) = 100 \times \text{SQRT}(0.009721) = 9.86 \%$

DIFFERENCE = TEST - REFERENCE = 6.898011 - 6.983973 = -.085963

SE DIFFERENCE = 0.026853

AUCINF RATIO = $100 \times e^{(\text{difference})}$ = $100 \times e^{(6.898011 - 6.983973)}$ = 91.76 %

90% GEOMETRIC CONFIDENCE INTERVAL

LOWER, UPPER = $100 \times e^{(\text{difference} \pm t_{0.05, 25} \times \text{SE difference})}$

LOWER = $100 \times e^{(-.085963 - 1.7081 \times 0.026853)}$ = 87.65 %

UPPER = $100 \times e^{(-.085963 + 1.7081 \times 0.026853)}$ = 96.07 %

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILGL2)
 TABLE 3. 11.

PEAK PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS

SUBJECT No.	C_{max} (ng/mL)				RATIO% #	LOG SCALE		
	CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg	DIFF			CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg	DIFF *
01	33.39	42.11	-8.71	79.30	3.5083	3.7402	-0.2319	
03	54.53	57.85	-3.32	94.26	3.9988	4.0579	-0.0591	
04	40.32	39.09	1.23	103.15	3.6968	3.6658	0.0310	
05	41.68	37.64	4.03	110.71	3.7299	3.6282	0.1018	
06	23.50	22.99	0.50	102.19	3.1569	3.1352	0.0216	
07	39.48	33.02	6.46	119.57	3.6758	3.4971	0.1788	
08	23.69	28.38	-4.69	83.46	3.1650	3.3458	-0.1807	
09	53.84	64.12	-10.28	83.97	3.9861	4.1608	-0.1747	
10	20.78	21.37	-0.59	97.23	3.0340	3.0621	-0.0281	
11	34.17	47.60	-13.43	71.78	3.5313	3.8629	-0.3315	
12	27.03	22.57	4.46	119.75	3.2969	3.1167	0.1802	
13	19.45	20.17	-0.73	96.41	2.9676	3.0042	-0.0366	
14	34.13	36.30	-2.17	94.03	3.5303	3.5918	-0.0615	
15	26.60	30.24	-3.64	87.95	3.2808	3.4092	-0.1284	
16	33.29	38.88	-5.59	85.62	3.5053	3.6606	-0.1552	
17	38.75	30.12	8.63	128.65	3.6571	3.4051	0.2520	
18	35.40	27.80	7.60	127.35	3.5666	3.3249	0.2417	
19	44.00	50.41	-6.41	87.28	3.7841	3.9201	-0.1360	
20	43.24	35.31	7.93	122.46	3.7667	3.5642	0.2026	
21	32.27	33.12	-0.84	97.45	3.4742	3.5000	-0.0258	
22	32.28	41.62	-9.35	77.54	3.4743	3.7286	-0.2543	
23	33.73	36.61	-2.88	92.15	3.5185	3.6003	-0.0818	
24	34.56	40.78	-6.22	84.74	3.5427	3.7083	-0.1656	
25	31.78	30.85	0.94	103.04	3.4589	3.4290	0.0299	
26	36.90	53.96	-17.05	68.39	3.6083	3.9882	-0.3799	
27	50.98	45.89	5.09	111.09	3.9314	3.8262	0.1052	
28	31.17	36.37	-5.19	85.72	3.4395	3.5936	-0.1541	
MEAN	35.22	37.23	-2.01	96.86	3.5291	3.5751	-0.0459	
SD(±)	9.07	11.01	6.60	16.65	0.2627	0.2973	0.1706	
C.V.(%)	25.74	29.59	328.51	17.19	7.4435	8.3146	371.3930	
Range (Min.)	19.45	20.17	-17.05	68.39	2.9676	3.0042	-0.3799	
(Max.)	54.53	64.12	8.63	128.65	3.9988	4.1608	0.2520	
Num of subjects	27	27	27	27	27	27	27	
Geometric Mean					34.0933	35.6982		

RATIO% = (CARTIA XT™ / CARDIZEM® CD) × 100
 * DIFF(Log Scale) = ln(CARTIA XT™) - ln(CARDIZEM® CD)
 N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 12.

ANOVA ON DESMETHYLDILTIAZEM LOG C_{max}

The GLM Procedure

Dependent Variable: lc_{max}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	3.74367805	0.13370279	8.88	<.0001
Error	25	0.37630483	0.01505219		
Corrected Total	53	4.11998289			

R-Square	Coeff Var	Root MSE	lc _{max} Mean
0.908663	3.453949	0.122687	3.552090

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.13731954	0.13731954	9.12	0.0057
subj(sq)	25	3.57565841	0.14302634	9.50	<.0001
peri	1	0.00220317	0.00220317	0.15	0.7053
drug	1	0.02787433	0.02787433	1.85	0.1857

The GLM Procedure
 Least Squares Means

drug	lc _{max} LSMEAN	Standard Error	Pr > t
A	3.52748562	0.02362741	<.0001
B	3.57295651	0.02362741	<.0001

sq	lc _{max} LSMEAN	Standard Error	Pr > t
AB	3.49975873	0.02406097	<.0001
BA	3.60068341	0.02318574	<.0001

peri	lc _{max} LSMEAN	Standard Error	Pr > t
1	3.55661289	0.02362741	<.0001
2	3.54382924	0.02362741	<.0001

The GLM Procedure

Dependent Variable: lc_{max}

Tests of Hypotheses Using the Type III MS for subj(sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.13731954	0.13731954	0.96	0.3365

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	-0.04547089	0.03341420	-1.36	0.1857

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 14.

TIME TO REACH PEAK PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS

T_{max} (hrs.)

SUBJECT No.	CARTIA XT™ 1 x 300 mg	CARDIZEM® CD 1 x 300 mg
01	16.00	14.00
03	18.00	18.00
04	16.03	24.00
05	18.00	16.00
06	16.00	24.00
07	16.00	15.00
08	9.00	7.00
09	18.00	16.00
10	6.00	18.00
11	16.00	18.00
12	16.00	6.00
13	6.00	16.00
14	16.00	16.00
15	15.00	13.00
16	16.00	14.00
17	15.00	18.00
18	18.00	5.00
19	15.00	18.00
20	18.00	16.00
21	15.00	6.00
22	18.02	18.00
23	9.00	5.02
24	18.00	18.00
25	16.00	16.00
26	18.00	16.00
27	18.00	18.00
28	10.00	18.00
MEDIAN	16.00	16.00
MEAN	15.04	15.07
SD (±)	3.66	5.12
C.V. (%)	24.37	33.96
Range (Min.)	6.00	5.00
(Max.)	18.02	24.00
Num of subjects	27	27

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 15.

ANOVA ON DESMETHYLDILTIAZEM T_{max}

The GLM Procedure

Dependent Variable: t_{max}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	643.411862	22.978995	1.48	0.1612
Error	25	387.248981	15.489959		
Corrected Total	53	1030.660844			

R-Square	Coeff Var	Root MSE	t_{max} Mean
0.624271	26.13923	3.935729	15.05679

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	37.4177018	37.4177018	2.42	0.1327
subj (sq)	25	565.0756418	22.6030257	1.46	0.1755
peri	1	40.9012142	40.9012142	2.64	0.1167
drug	1	0.0111114	0.0111114	0.00	0.9788

The GLM Procedure
Least Squares Means

drug	t_{max} LSMEAN	Standard Error	Pr > t
A	15.0402930	0.7579513	<.0001
B	15.0115842	0.7579513	<.0001

sq	t_{max} LSMEAN	Standard Error	Pr > t
AB	14.1929487	0.7718599	<.0001
BA	15.8589286	0.7437828	<.0001

peri	t_{max} LSMEAN	Standard Error	Pr > t
1	15.8968407	0.7579513	<.0001
2	14.1550366	0.7579513	<.0001

The GLM Procedure

Dependent Variable: t_{max}

Tests of Hypotheses Using the Type III MS for subj (sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	37.41770183	37.41770183	1.66	0.2100

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	0.02870879	1.07190508	0.03	0.9788

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 16.

THE APPARENT HALF-LIFE OF DESMETHYLDILTIAZEM

$T_{1/2}$ (hrs.)

SUBJECT No.	CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg
01	12.51	8.91
03	10.72	9.95
04	14.90	15.10
05	9.82	9.99
06	15.05	9.99
07	10.20	9.65
08	8.71	10.37
09	9.56	9.80
10	8.74	8.72
11	10.90	12.89
12	9.02	10.81
13	11.50	12.78
14	12.43	13.28
15	12.16	13.93
16	9.06	9.70
17	10.05	10.22
18	9.10	9.16
19	12.71	12.09
20	8.59	8.45
21	8.74	11.44
22	11.22	11.24
23	11.36	12.47
24	13.06	12.64
25	8.23	8.75
26	8.69	8.54
27	10.44	13.14
28	17.72	11.79
MEAN	10.93	10.96
SD(±)	2.33	1.84
C.V.(%)	21.30	16.83
Range (Min.)	8.23	8.45
(Max.)	17.72	15.10
Num of subjects	27	27

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 17.

ANOVA ON DESMETHYLDILTIAZEM HALF-LIFE

The GLM Procedure

Dependent Variable: t_{half}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	178.5552388	6.3769728	3.13	0.0026
Error	25	50.8545336	2.0341813		
Corrected Total	53	229.4097724			

R-Square	Coeff Var	Root MSE	t_{half} Mean
0.778324	13.03183	1.426247	10.94434

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	11.1767221	11.1767221	5.49	0.0273
subj (sq)	25	164.5378858	6.5815154	3.24	0.0023
peri	1	2.8333659	2.8333659	1.39	0.2490
drug	1	0.0217618	0.0217618	0.01	0.9184

The GLM Procedure
Least Squares Means

drug	t_{half} LSMEAN	Standard Error	Pr > t
A	10.9073903	0.2746699	<.0001
B	10.9475674	0.2746699	<.0001

sq	t_{half} LSMEAN	Standard Error	Pr > t
AB	10.4722199	0.2797101	<.0001
BA	11.3827377	0.2695354	<.0001

peri	t_{half} LSMEAN	Standard Error	Pr > t
1	10.6982588	0.2746699	<.0001
2	11.1566988	0.2746699	<.0001

The GLM Procedure

Dependent Variable: t_{half}

Tests of Hypotheses Using the Type III MS for subj (sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	11.17672214	11.17672214	1.70	0.2044

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	-0.04017709	0.38844186	-0.10	0.9184

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 18.

THE ELIMINATION RATE CONSTANT OF DESMETHYLDILTIAZEM

SUBJECT No.	K_{el} (hour ⁻¹)	
	CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg
01	0.055	0.078
03	0.065	0.070
04	0.047	0.046
05	0.071	0.069
06	0.046	0.069
07	0.068	0.072
08	0.080	0.067
09	0.073	0.071
10	0.079	0.079
11	0.064	0.054
12	0.077	0.064
13	0.060	0.054
14	0.056	0.052
15	0.057	0.050
16	0.077	0.071
17	0.069	0.068
18	0.076	0.076
19	0.055	0.057
20	0.081	0.082
21	0.079	0.061
22	0.062	0.062
23	0.061	0.056
24	0.053	0.055
25	0.084	0.079
26	0.080	0.081
27	0.066	0.053
28	0.039	0.059
MEAN	0.066	0.065
SD(±)	0.012	0.011
C.V. (%)	18.518	16.271
Range (Min.)	0.039	0.046
(Max.)	0.084	0.082
Num of subjects	27	27

N.C. = No Calculation.

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 19.

ANOVA ON DESMETHYLDILTIAZEM K_{e1}

The GLM Procedure

Dependent Variable: k_{e1}

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	0.00552527	0.00019733	3.93	0.0005
Error	25	0.00125509	0.00005020		
Corrected Total	53	0.00678035			

R-Square	Coeff Var	Root MSE	k_{e1} Mean
0.814894	10.83398	0.007085	0.065400

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.00026684	0.00026684	5.32	0.0297
subj(sq)	25	0.00519681	0.00020787	4.14	0.0004
peri	1	0.00005117	0.00005117	1.02	0.3224
drug	1	0.00001221	0.00001221	0.24	0.6262

The GLM Procedure
 Least Squares Means

drug	k_{e1} LSMEAN	Standard Error	Pr > t
A	0.06595842	0.00136453	<.0001
B	0.06500668	0.00136453	<.0001

sq	k_{e1} LSMEAN	Standard Error	Pr > t
AB	0.06770702	0.00138957	<.0001
BA	0.06325808	0.00133902	<.0001

peri	k_{e1} LSMEAN	Standard Error	Pr > t
1	0.06645667	0.00136453	<.0001
2	0.06450843	0.00136453	<.0001

The GLM Procedure

Dependent Variable: k_{e1}

Tests of Hypotheses Using the Type III MS for subj (sq) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sq	1	0.00026684	0.00026684	1.28	0.2680

Parameter	Estimate	Standard Error	t Value	Pr > t
TEST - REF	0.00095174	0.00192974	0.49	0.6262

BIOVAIL CONTRACT RESEARCH
 A DIVISION OF BIOVAIL CORPORATION
 Study # 2443 (B01-527PK-DILG12)
 TABLE 3. 20.

THE CORRELATION COEFFICIENT (r value) OF THE MOST LINEAR PORTION
 OF THE TERMINAL ELIMINATION PHASE FOR PLASMA DESMETHYLDILTIAZEM

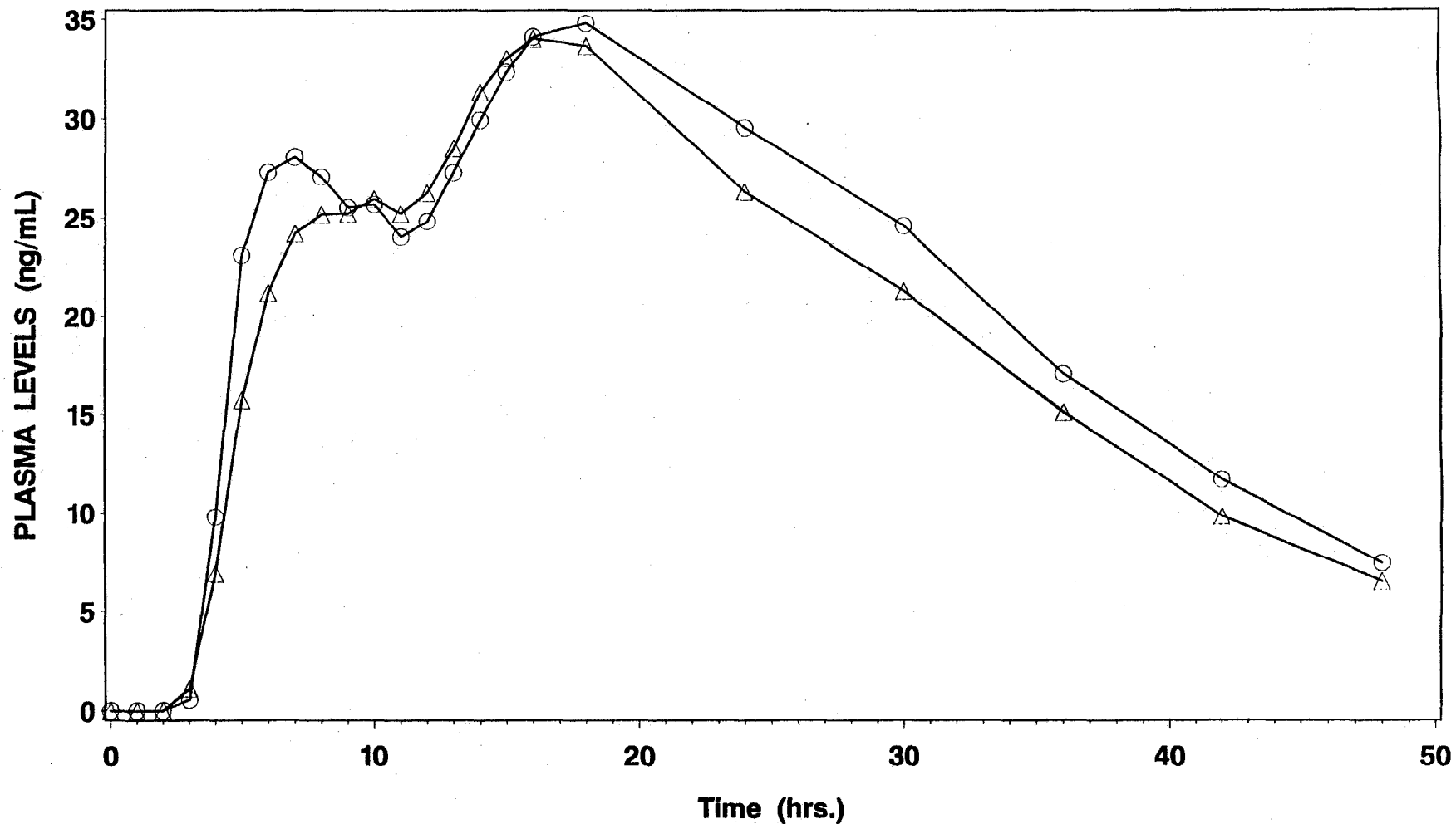
SUBJECT No.	CARTIA XT TM 1 x 300 mg	CARDIZEM [®] CD 1 x 300 mg
01	0.99524	0.99059
03	0.99711	0.99861
04	0.99975	0.98460
05	0.99888	0.99949
06	0.99841	0.99851
07	0.99956	0.99751
08	0.99694	0.99802
09	0.99489	0.99792
10	0.99401	0.99768
11	0.99762	0.98861
12	0.99630	0.98981
13	0.98932	0.97436
14	0.99835	0.99884
15	0.99779	0.99182
16	0.99888	0.99395
17	0.99023	0.99158
18	0.99922	0.99862
19	0.95778	0.98961
20	0.99582	0.99920
21	0.99967	0.99252
22	0.99099	0.99905
23	0.99593	0.99715
24	0.99828	0.99907
25	0.99997	0.99773
26	0.99922	0.99968
27	0.99499	0.99915
28	0.99662	0.99863
MEAN	0.99525	0.99490
SD (±)	0.00802	0.00588
C.V. (%)	0.80621	0.59087
Range (Min.)	0.95778	0.97436
(Max.)	0.99997	0.99968
Num of subjects	27	27

N.C. = No Calculation of K_{e1}

FIGURES

MEAN PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS

STUDY # 2443 (N=27)



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.1

SEMI LOG MEAN PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS

STUDY # 2443 (N=27)

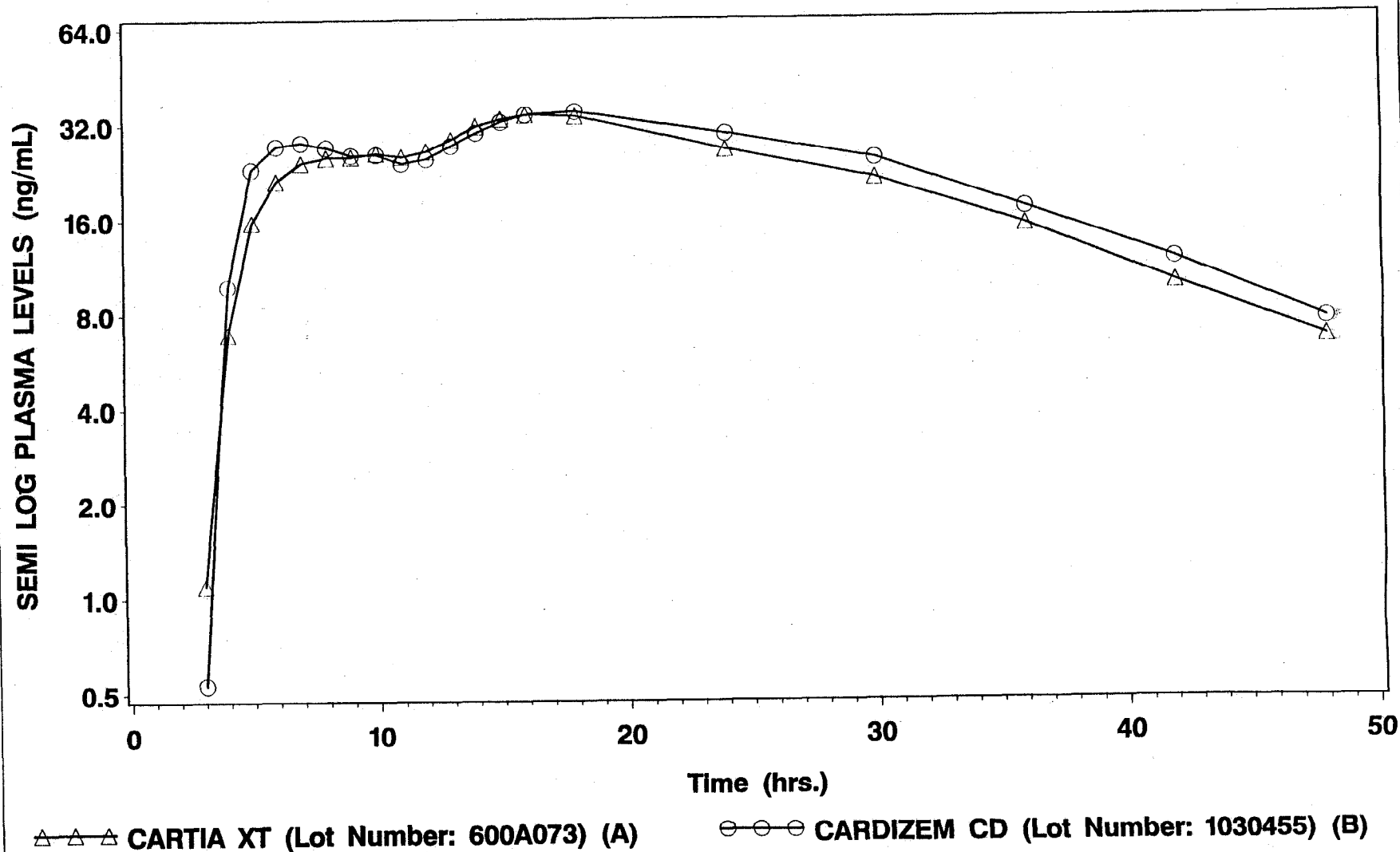
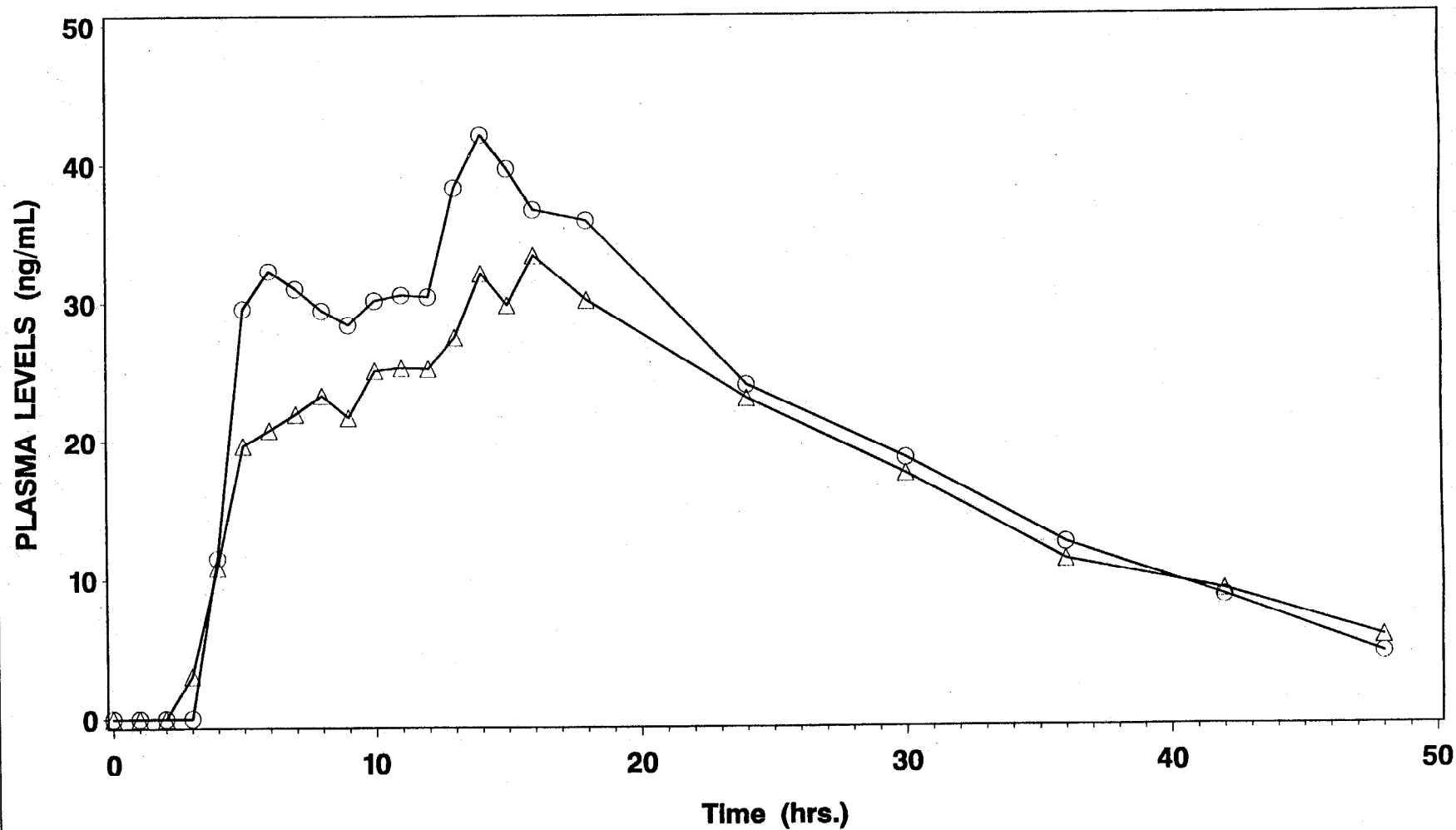


FIGURE 3.2

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 01



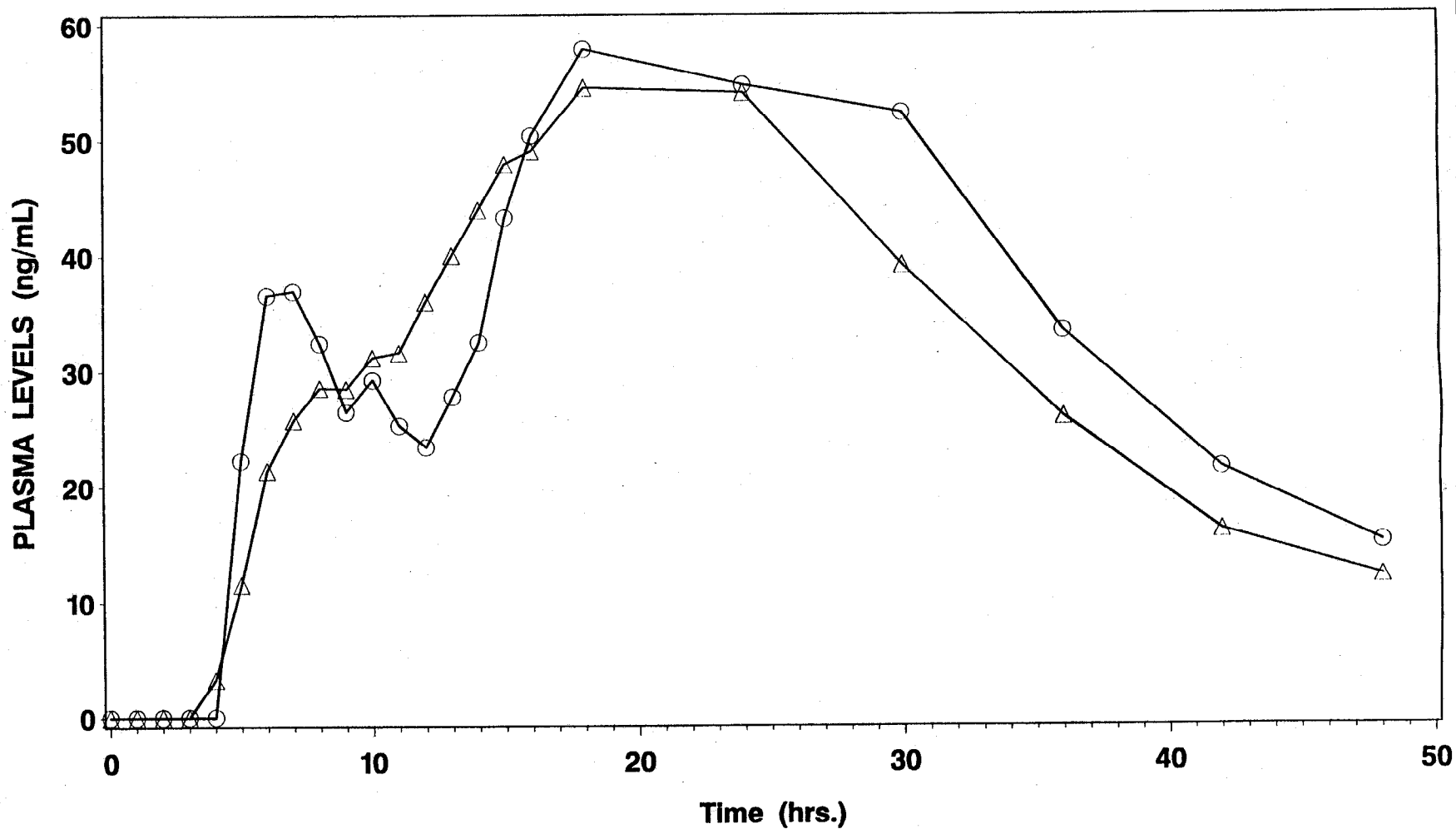
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.3

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 03



▲▲▲ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.4

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 04

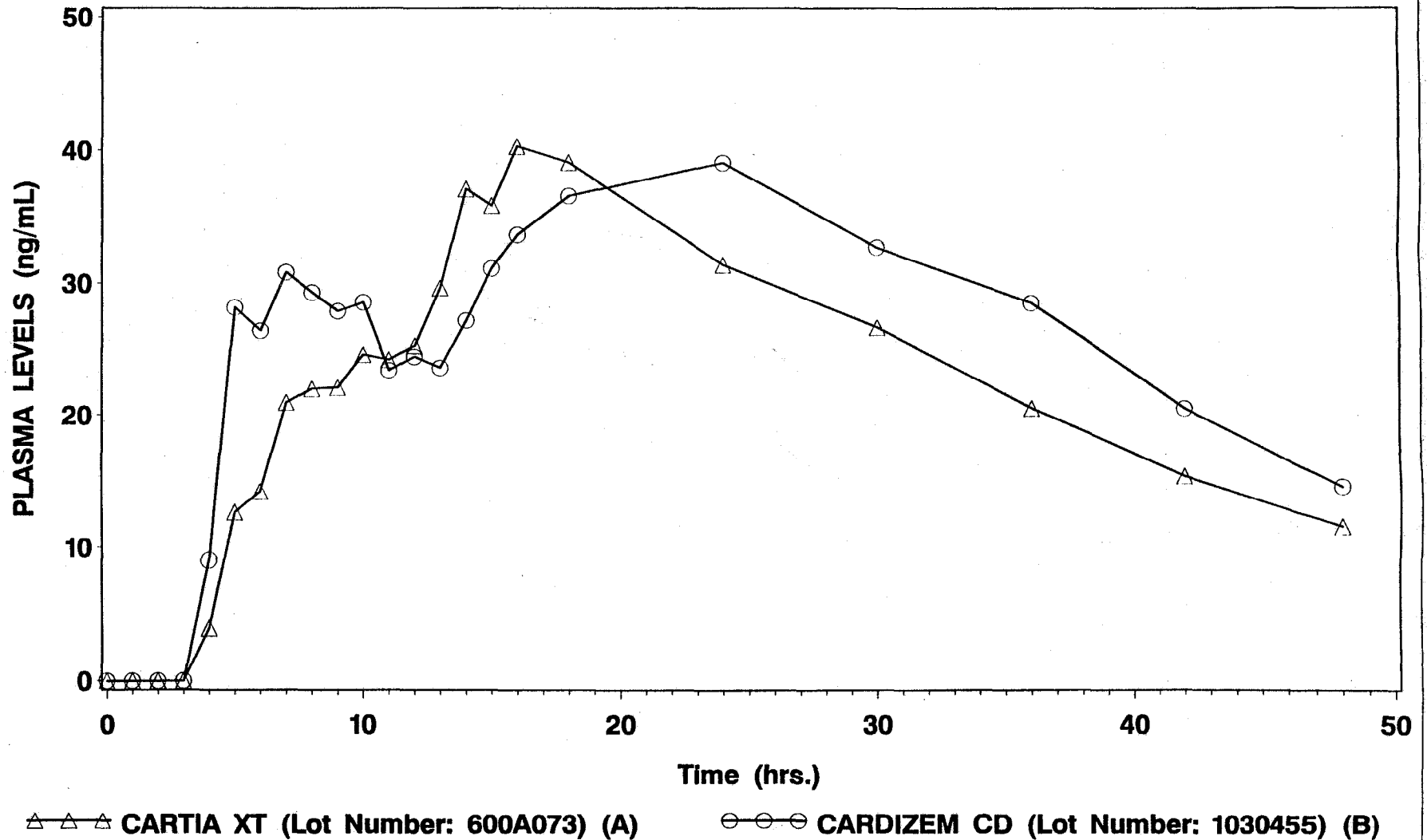
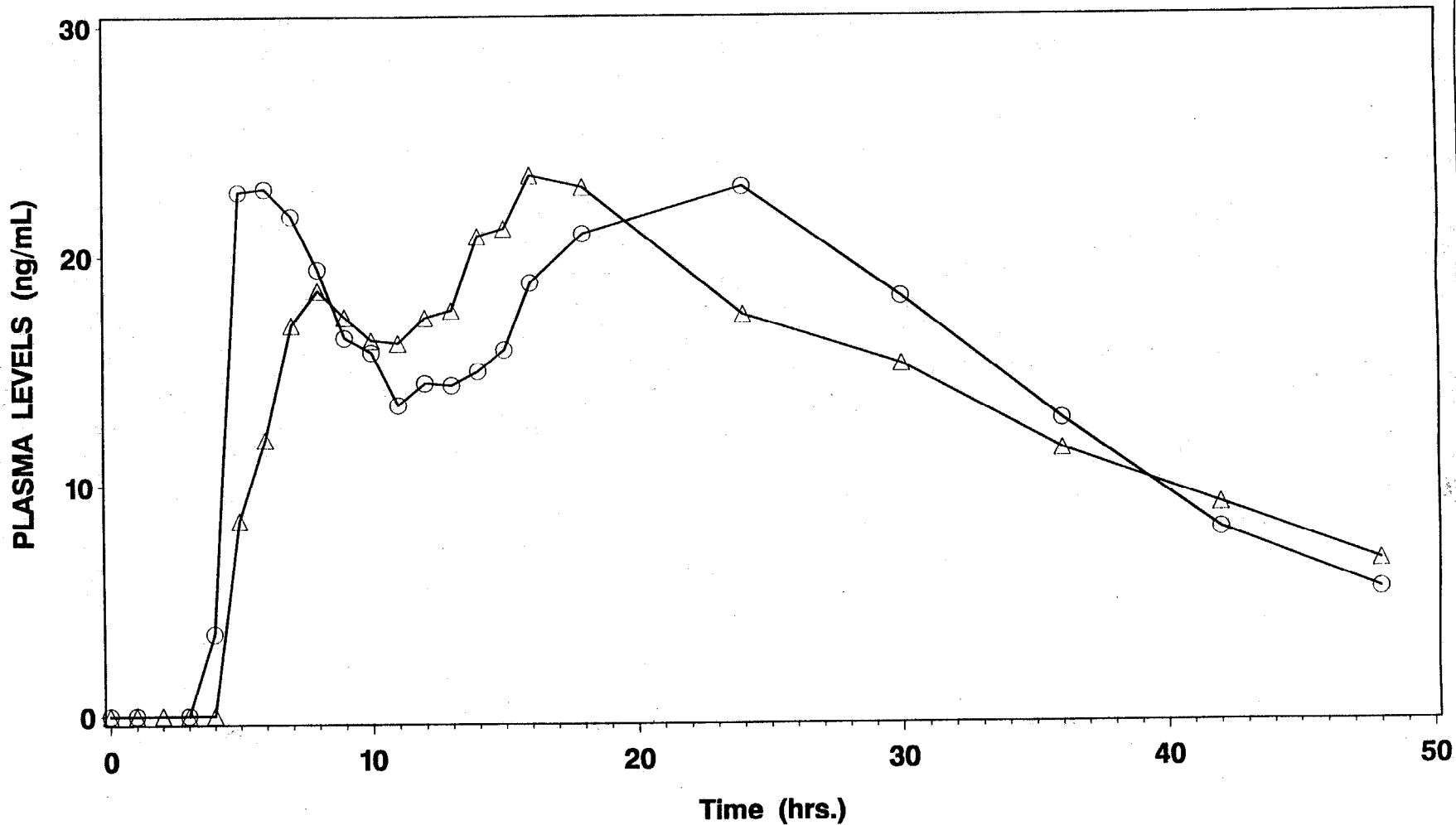


FIGURE 3.5

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 06



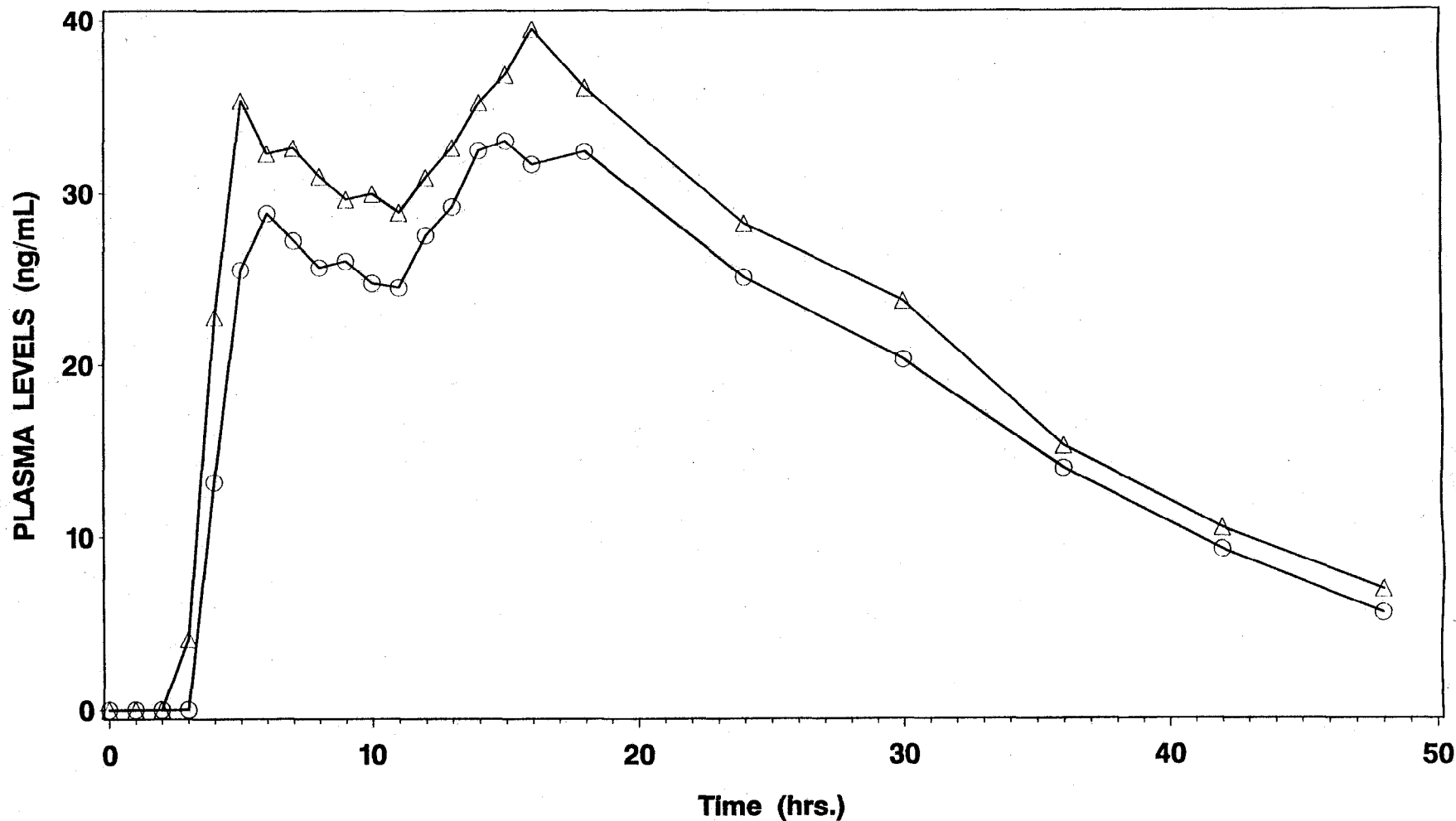
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.7

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 07



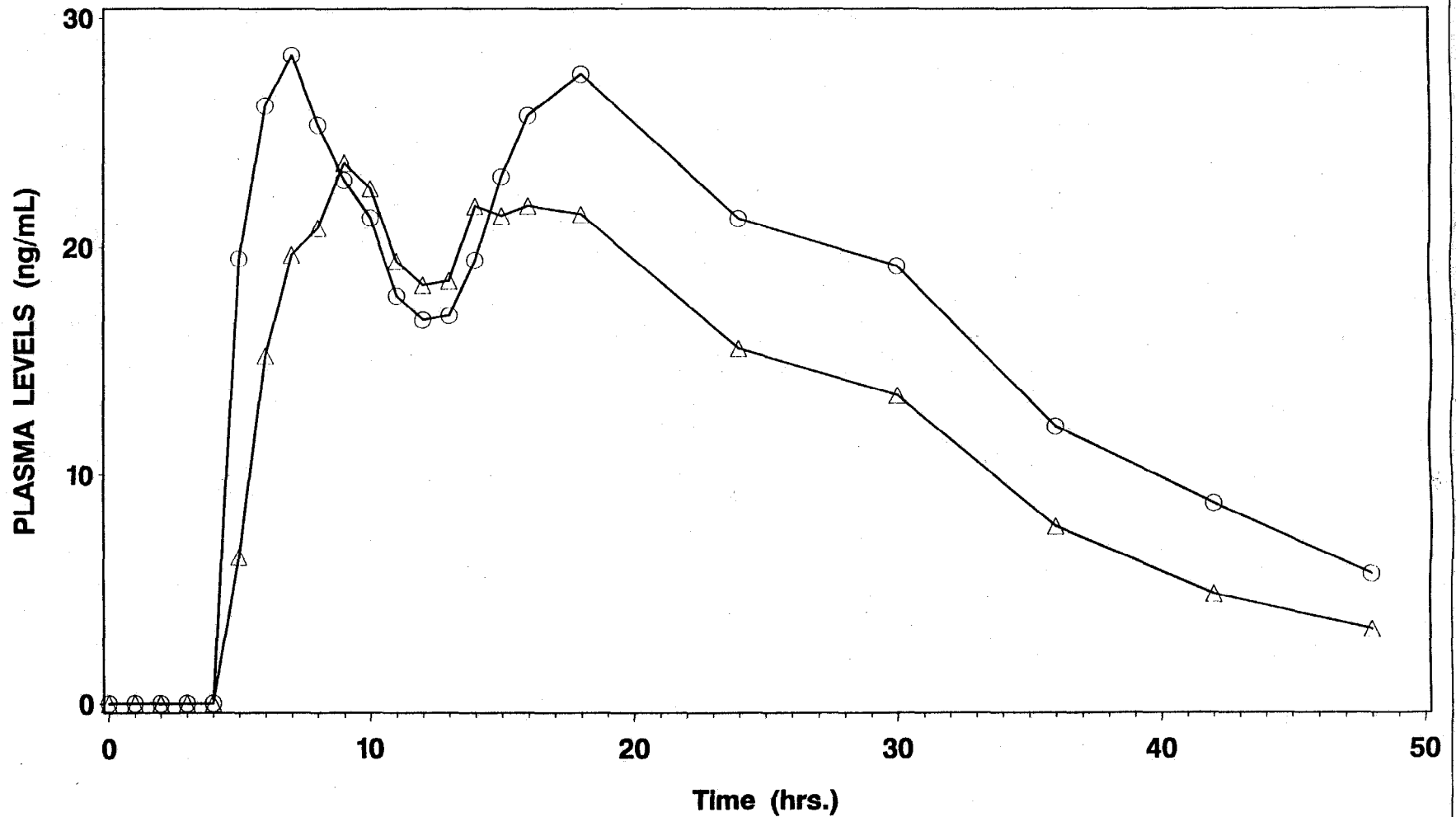
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.8

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 08



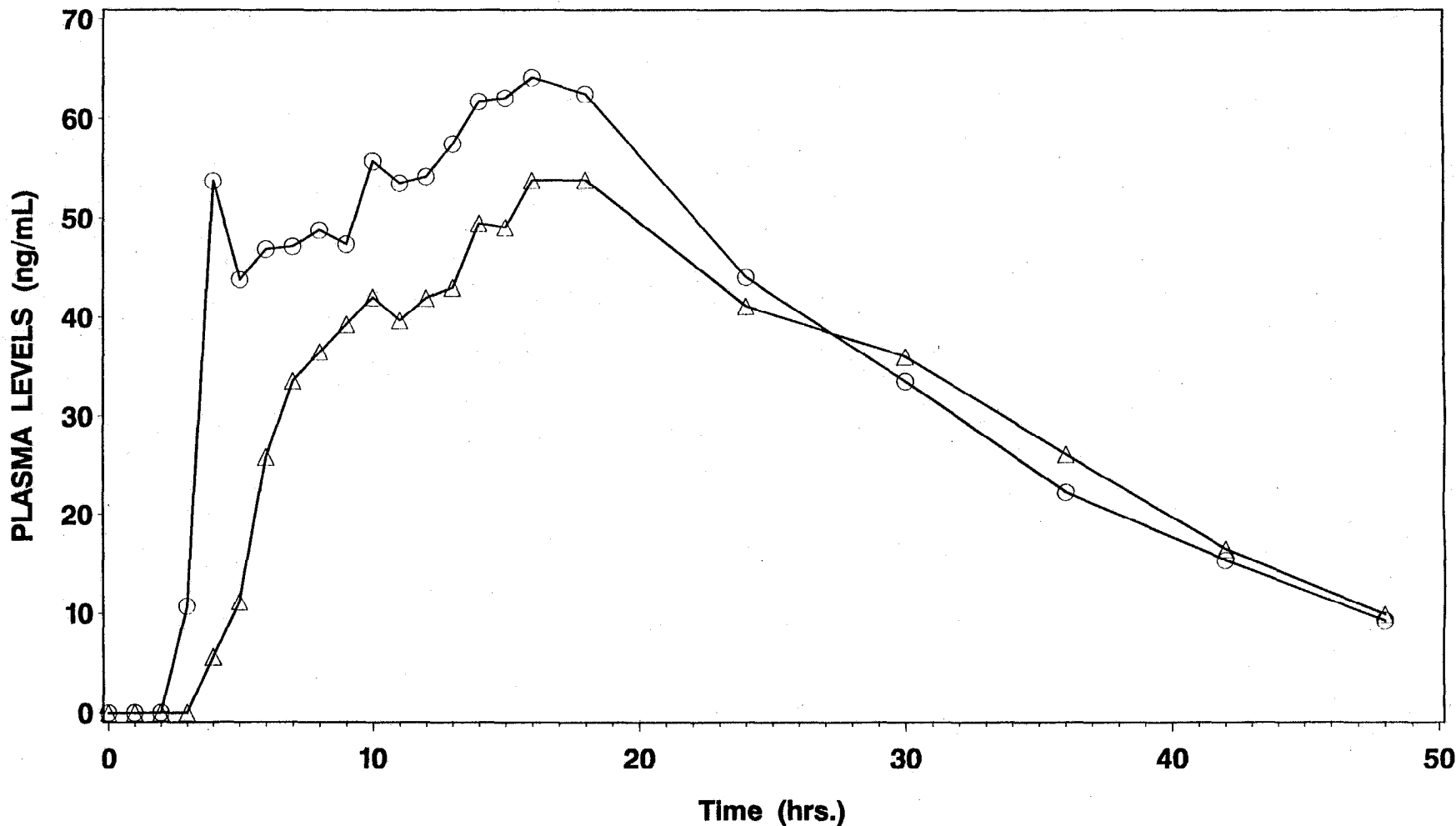
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.9

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 09



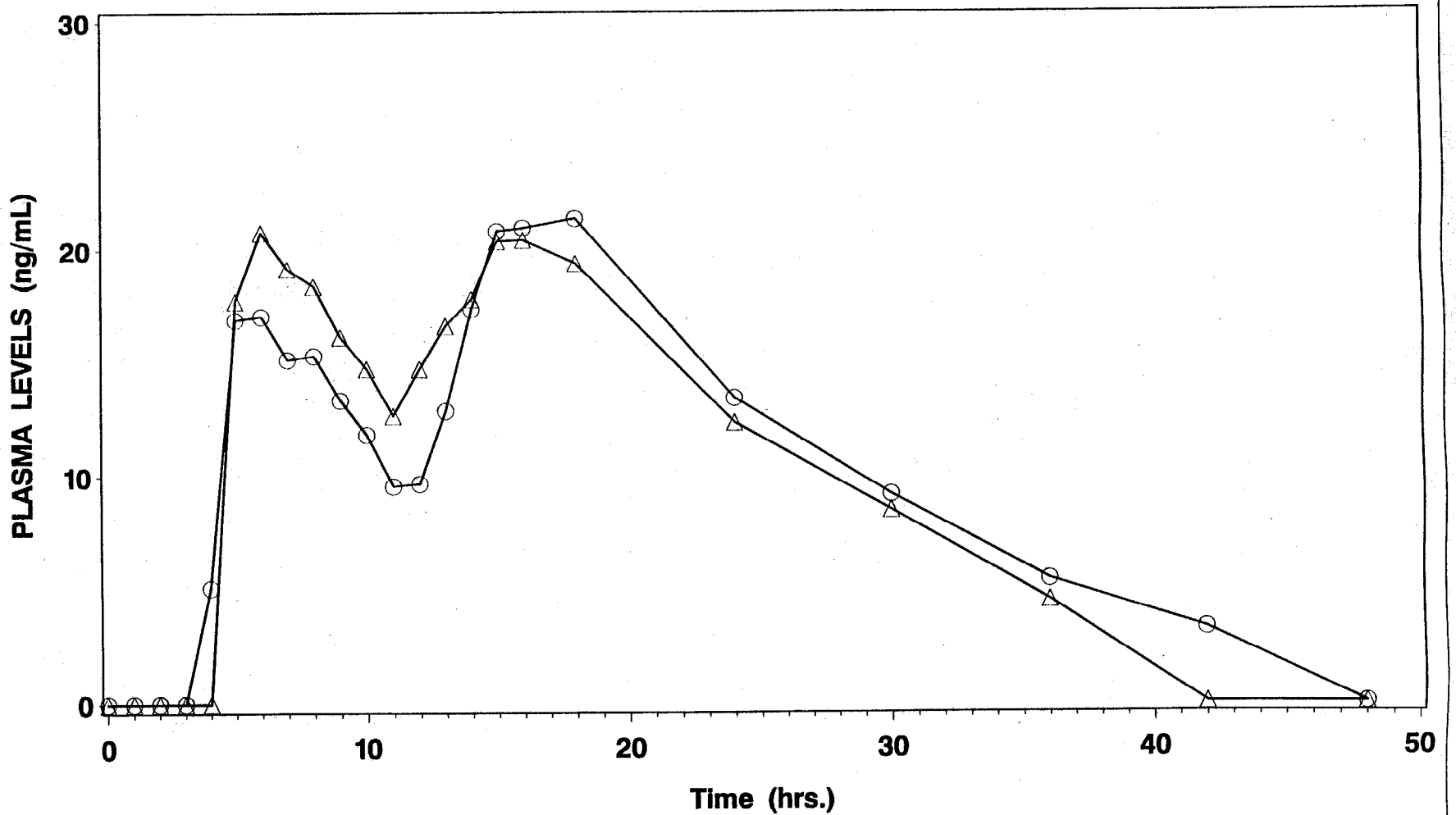
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.10

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 10



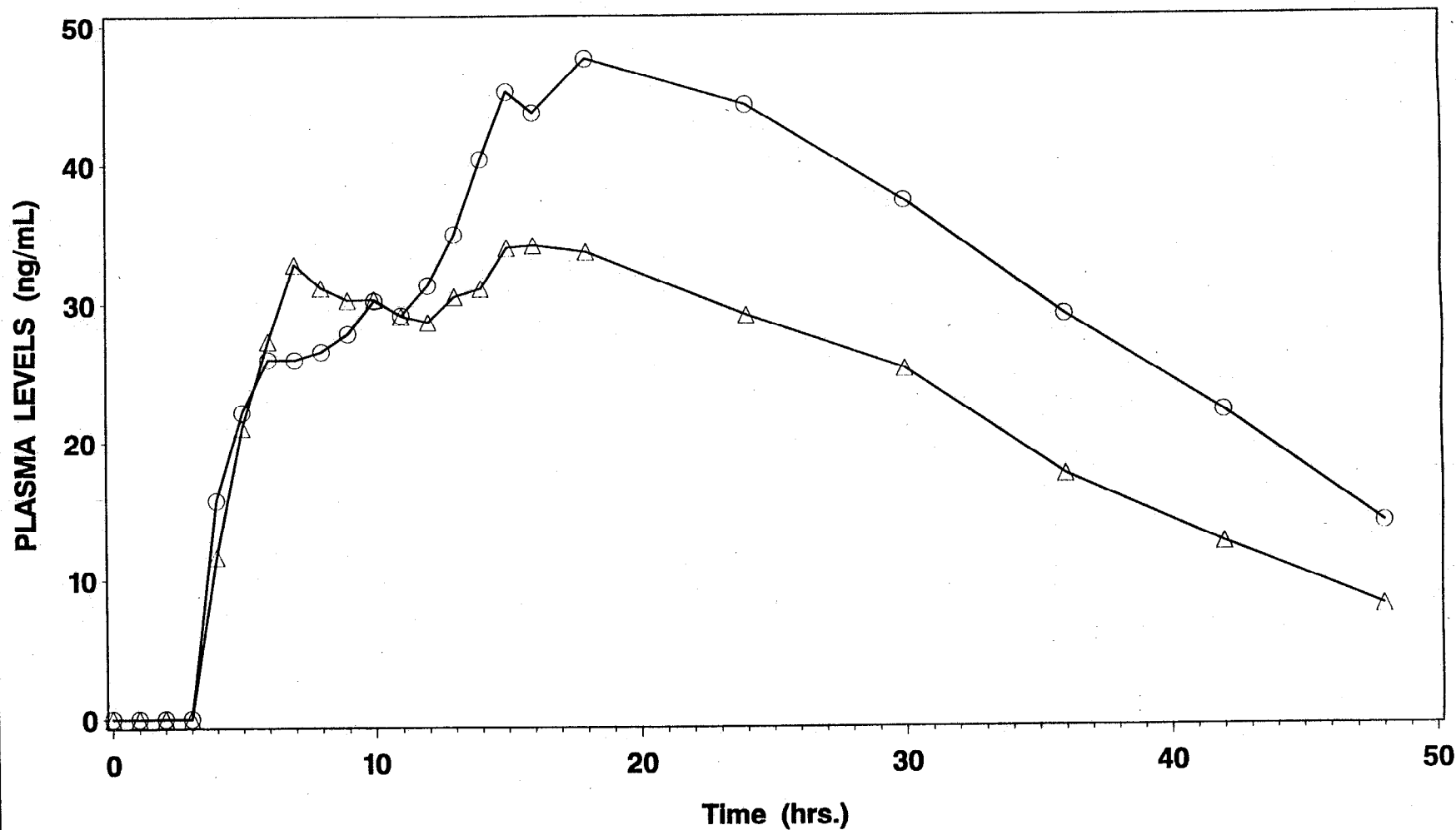
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.11

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 11



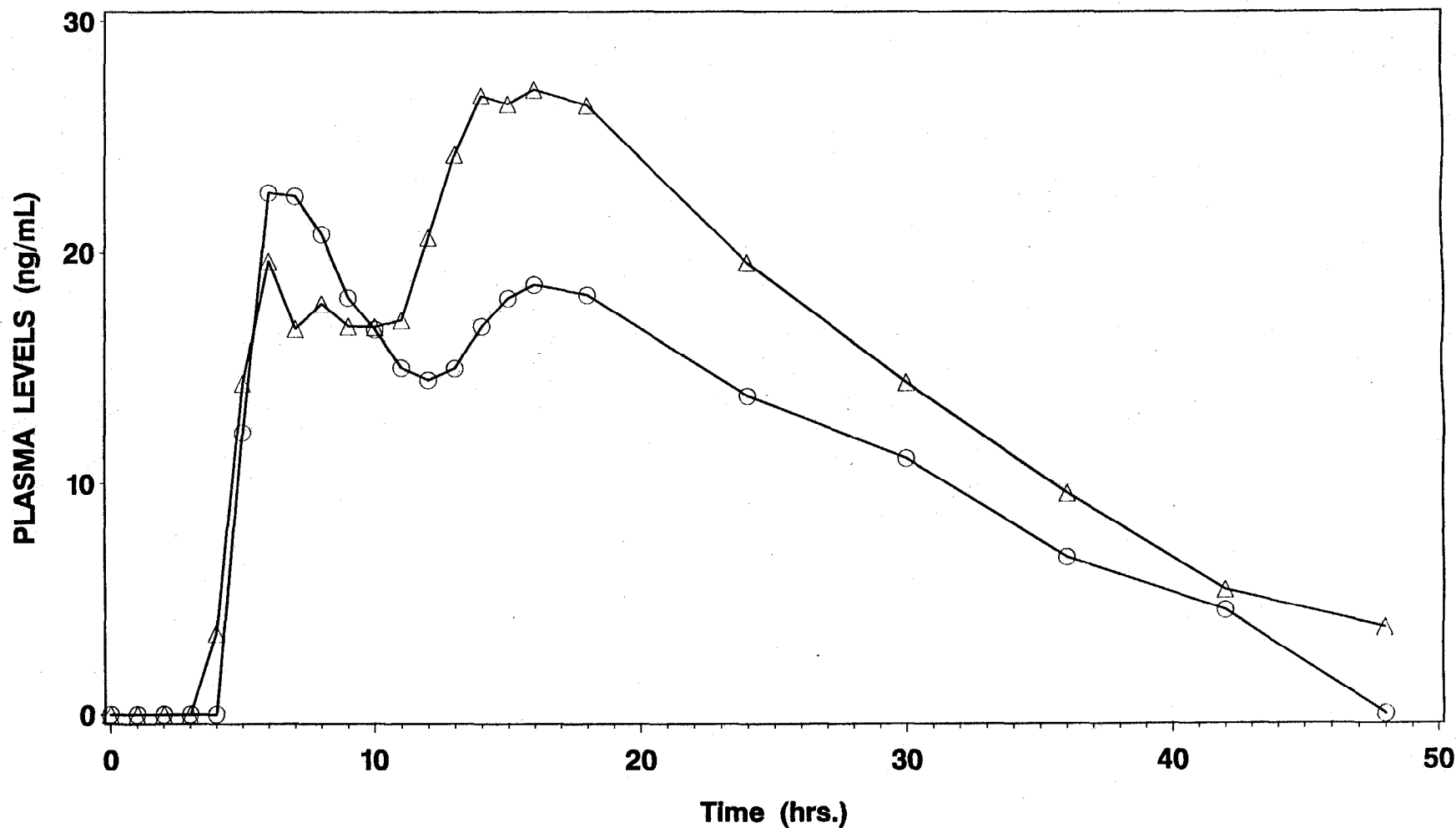
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.12

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 12



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

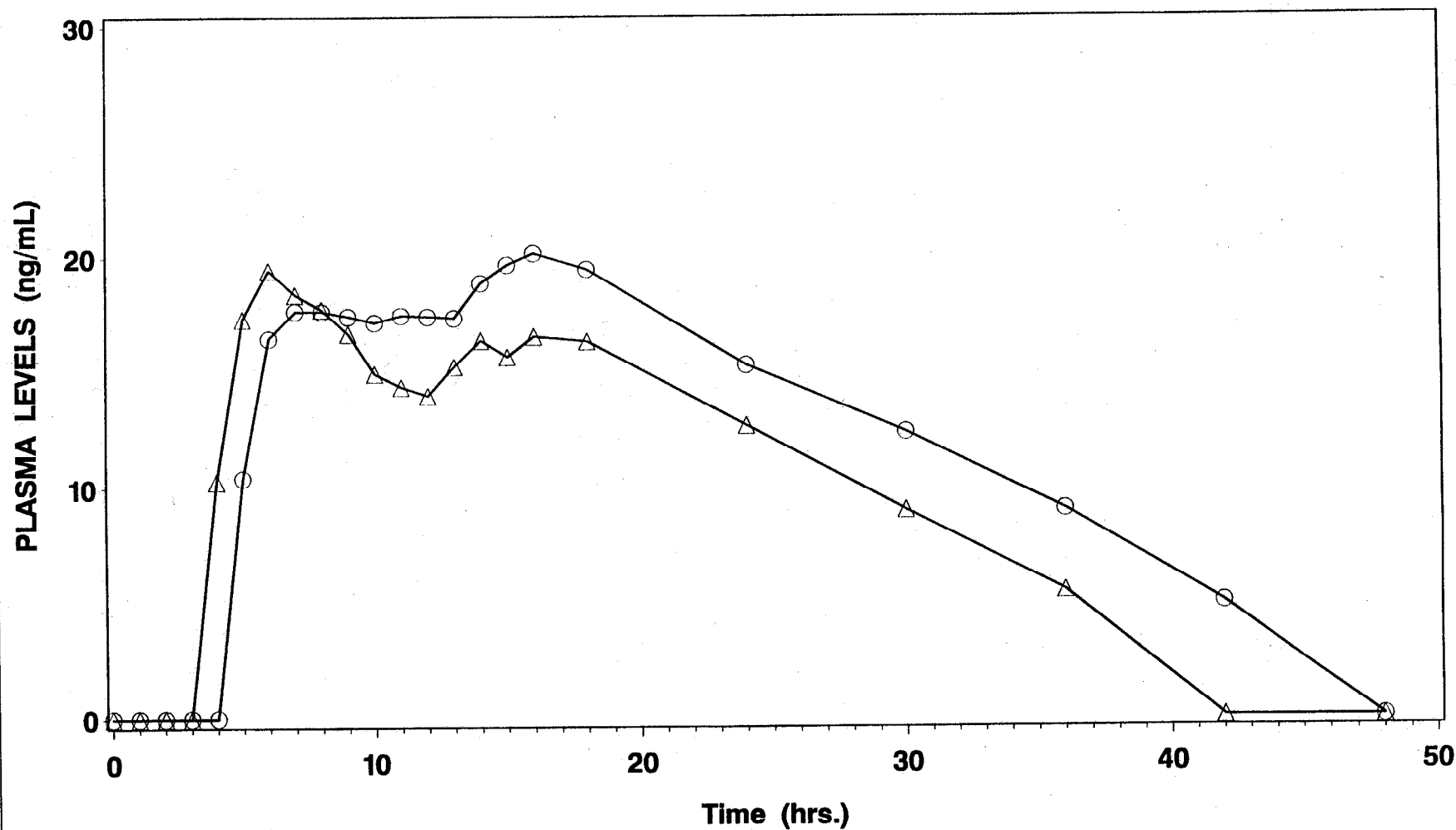
○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.13

33
11
00

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 13



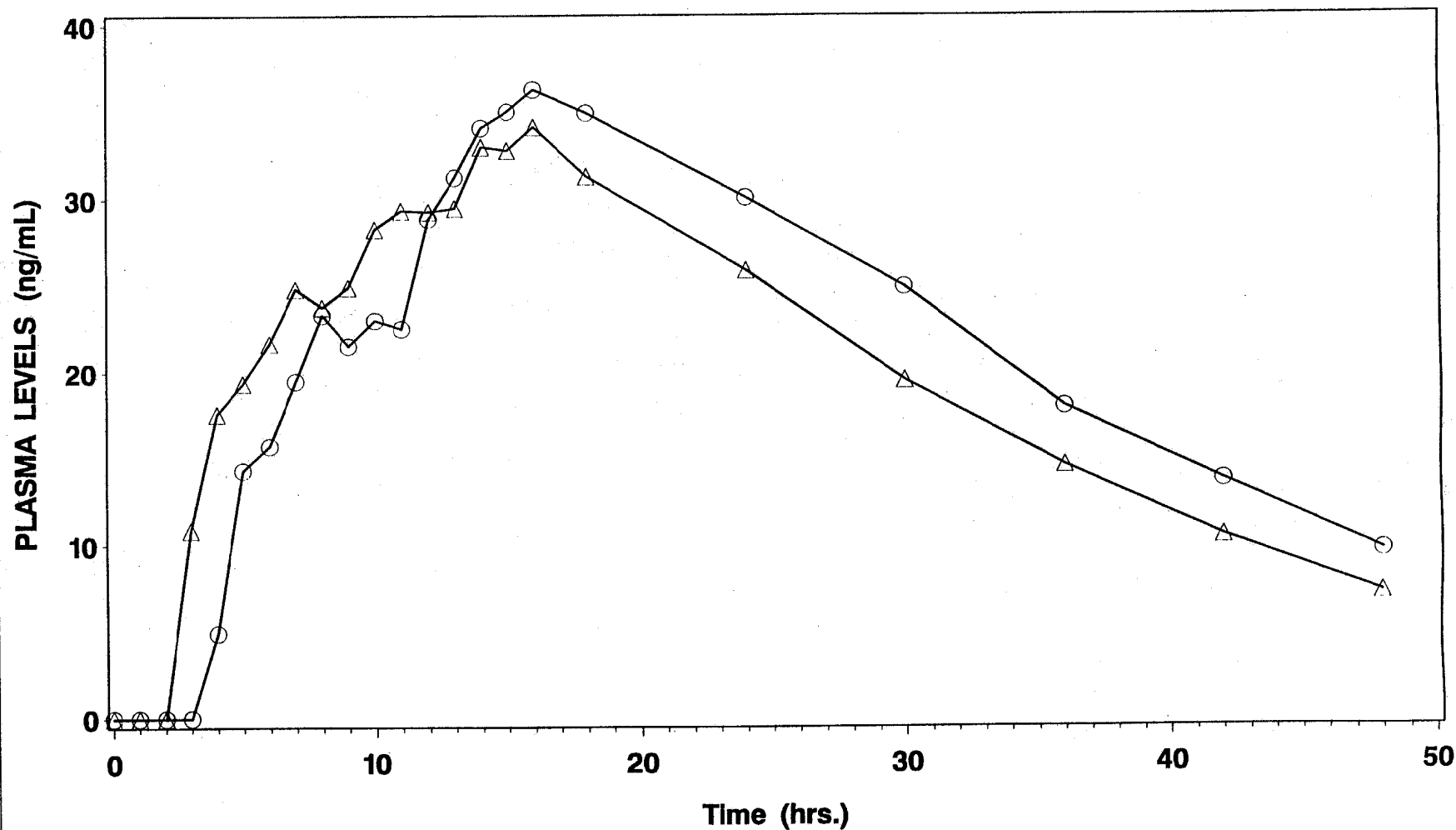
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.14

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 14



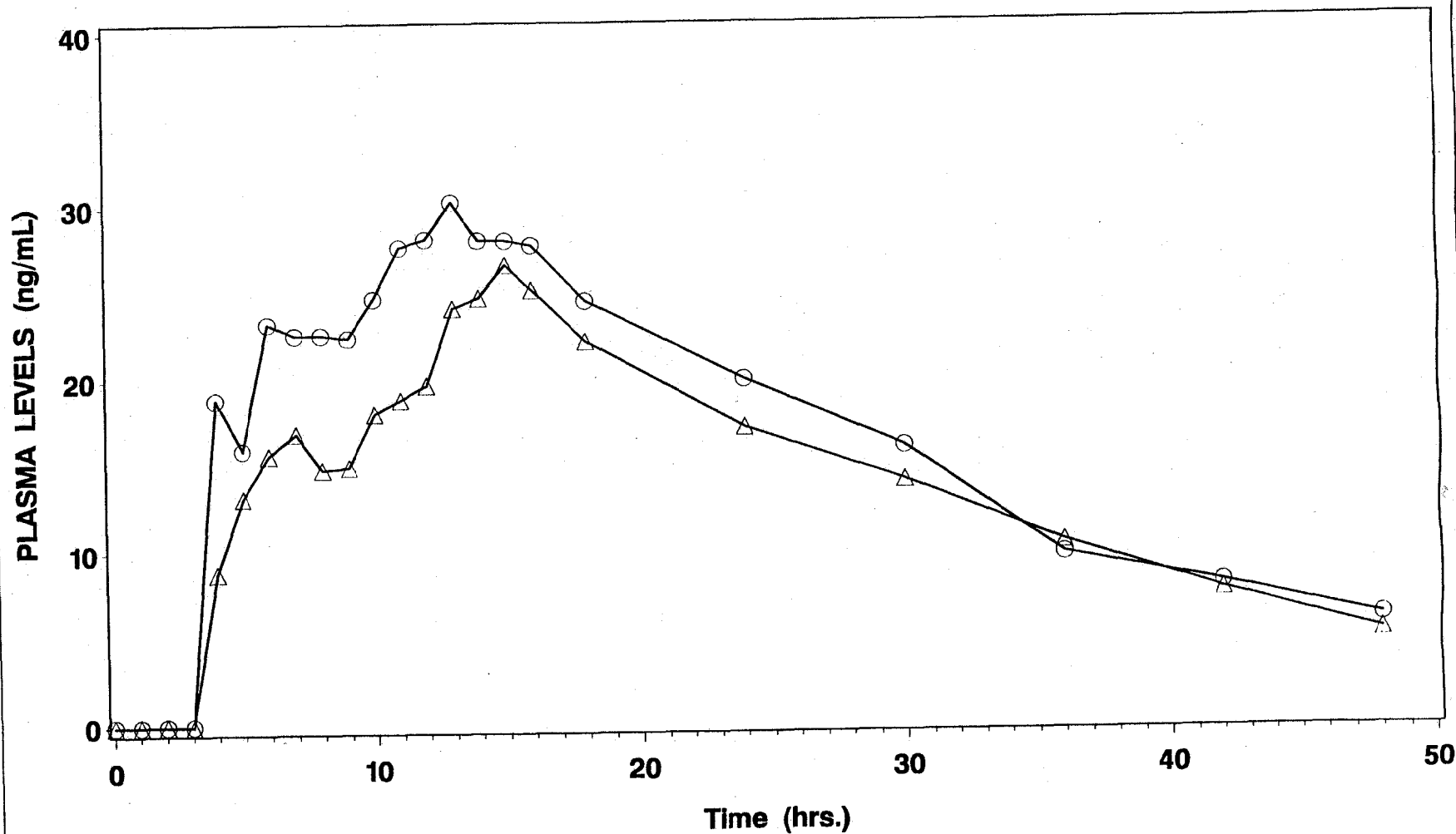
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.15

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 15



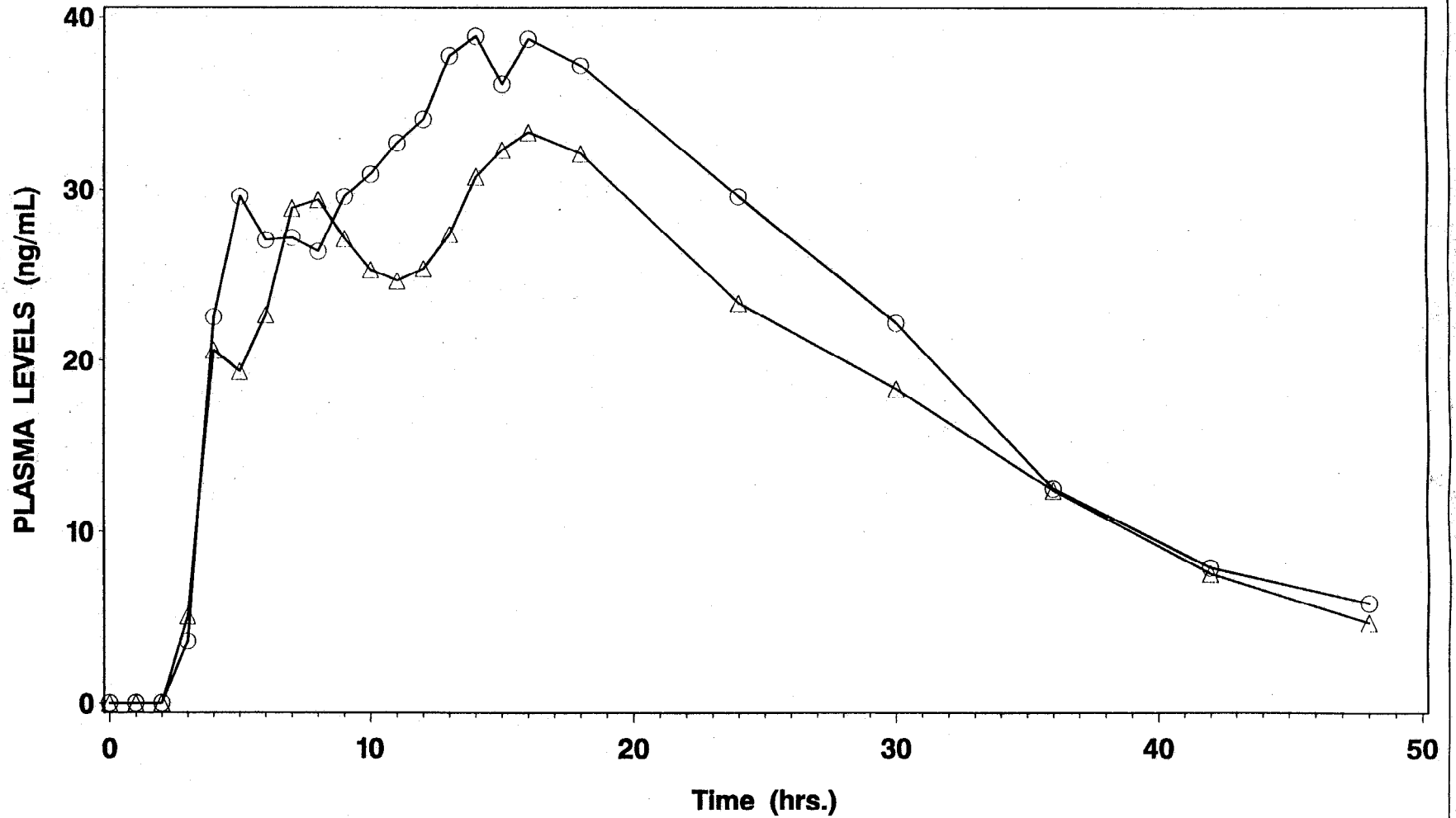
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.16

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 16



▲▲▲ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.17

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 17

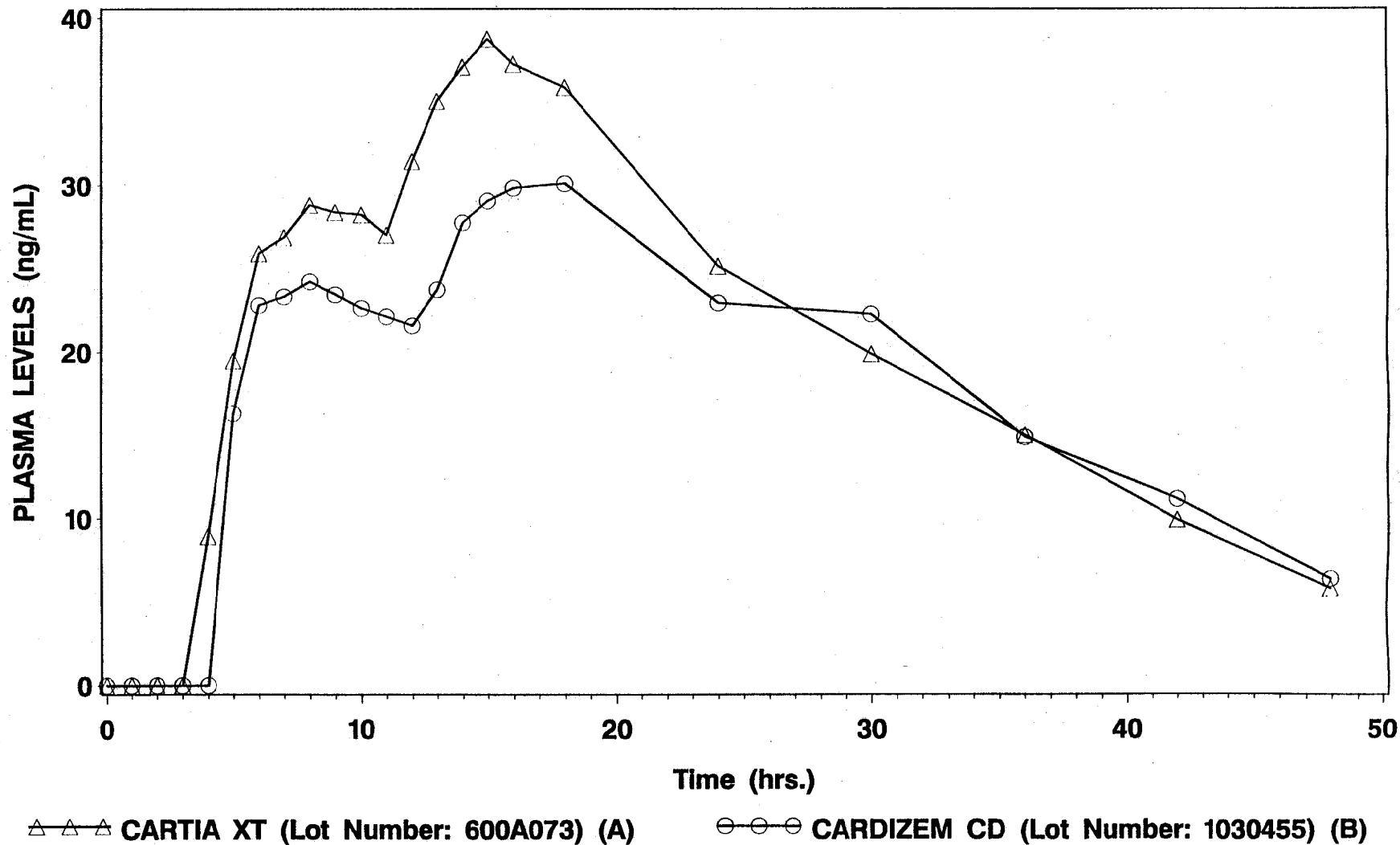
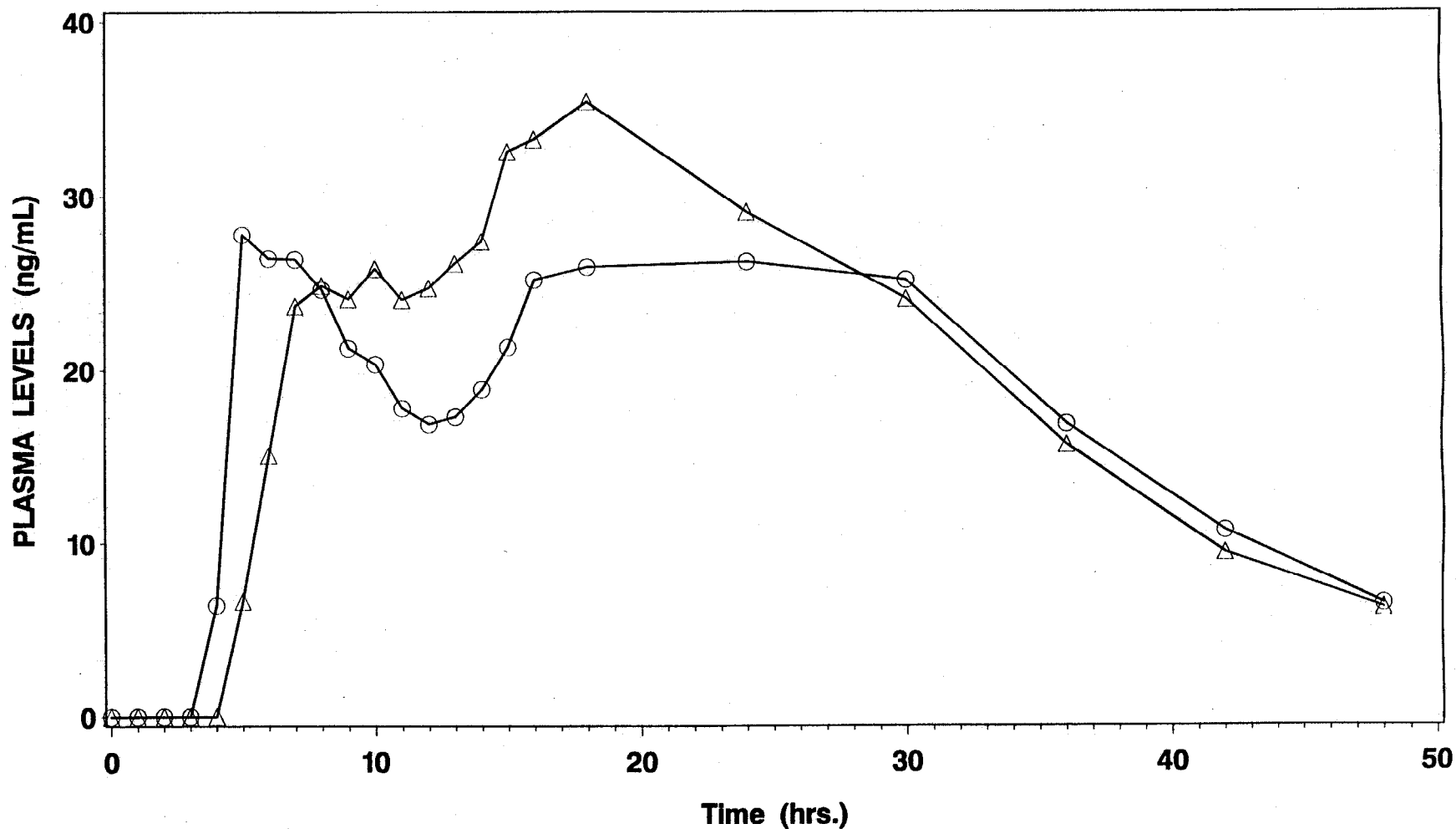


FIGURE 3.18

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 18



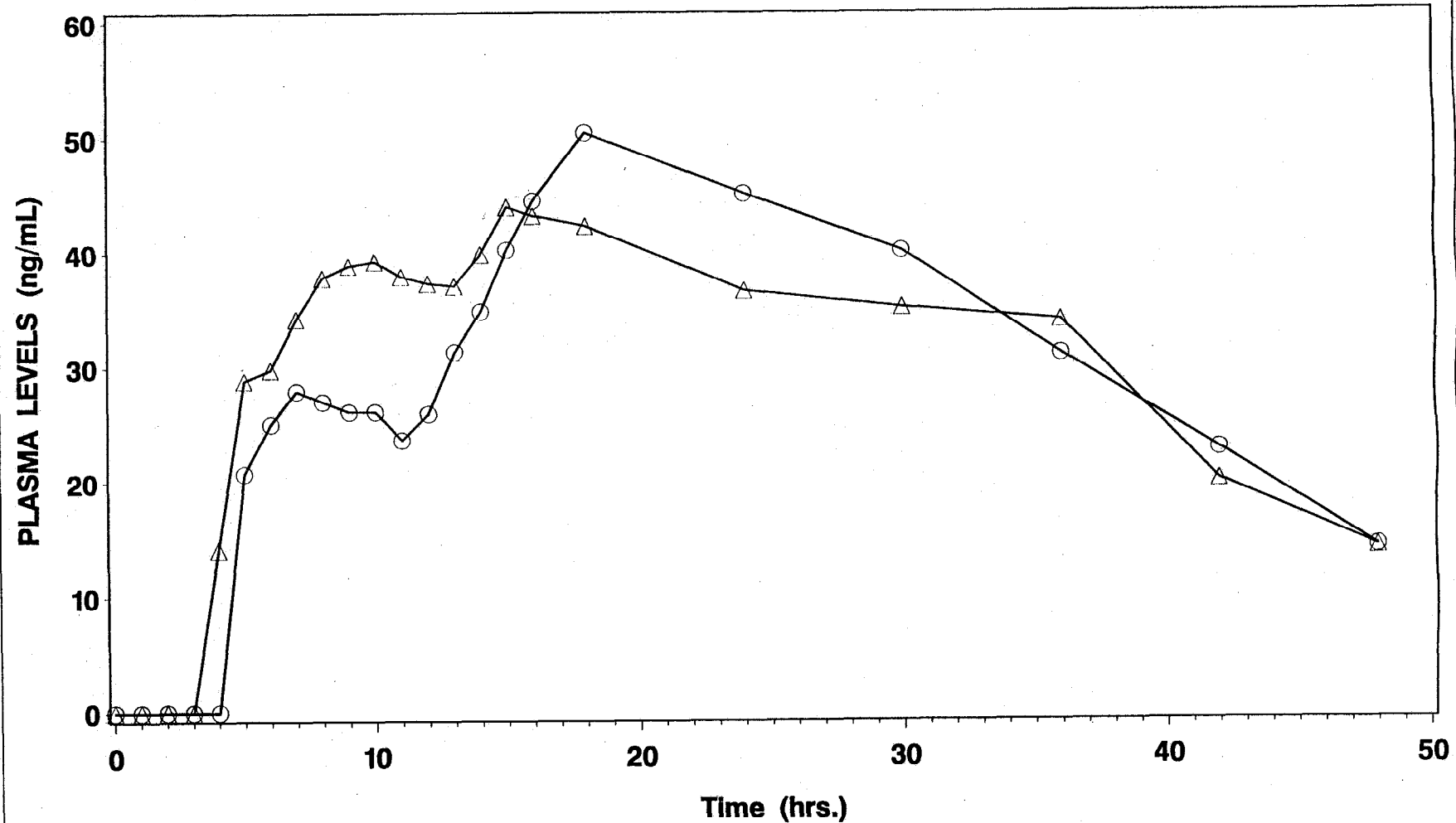
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.19

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 19



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

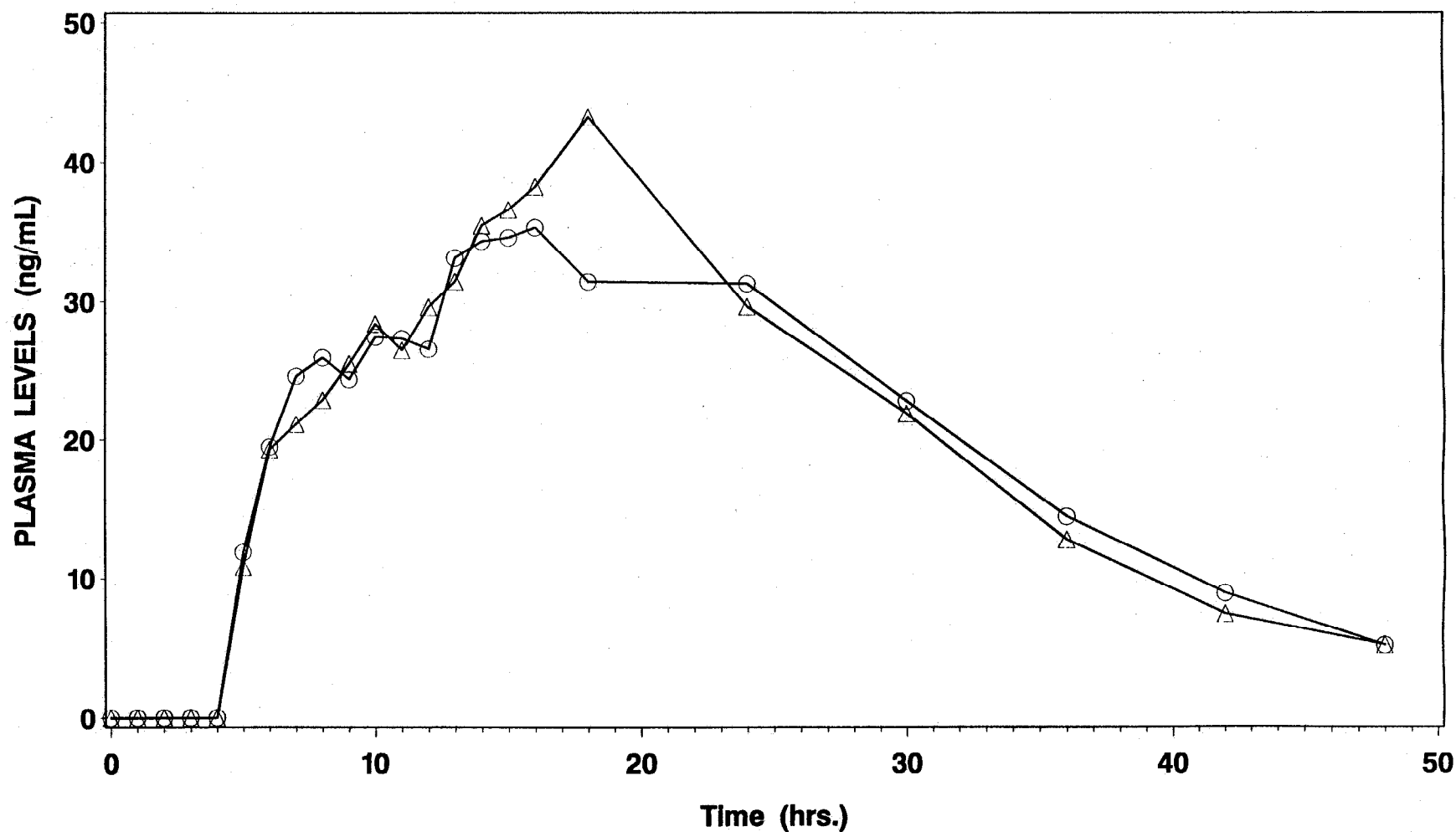
○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.20

322

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 20



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.21

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 21

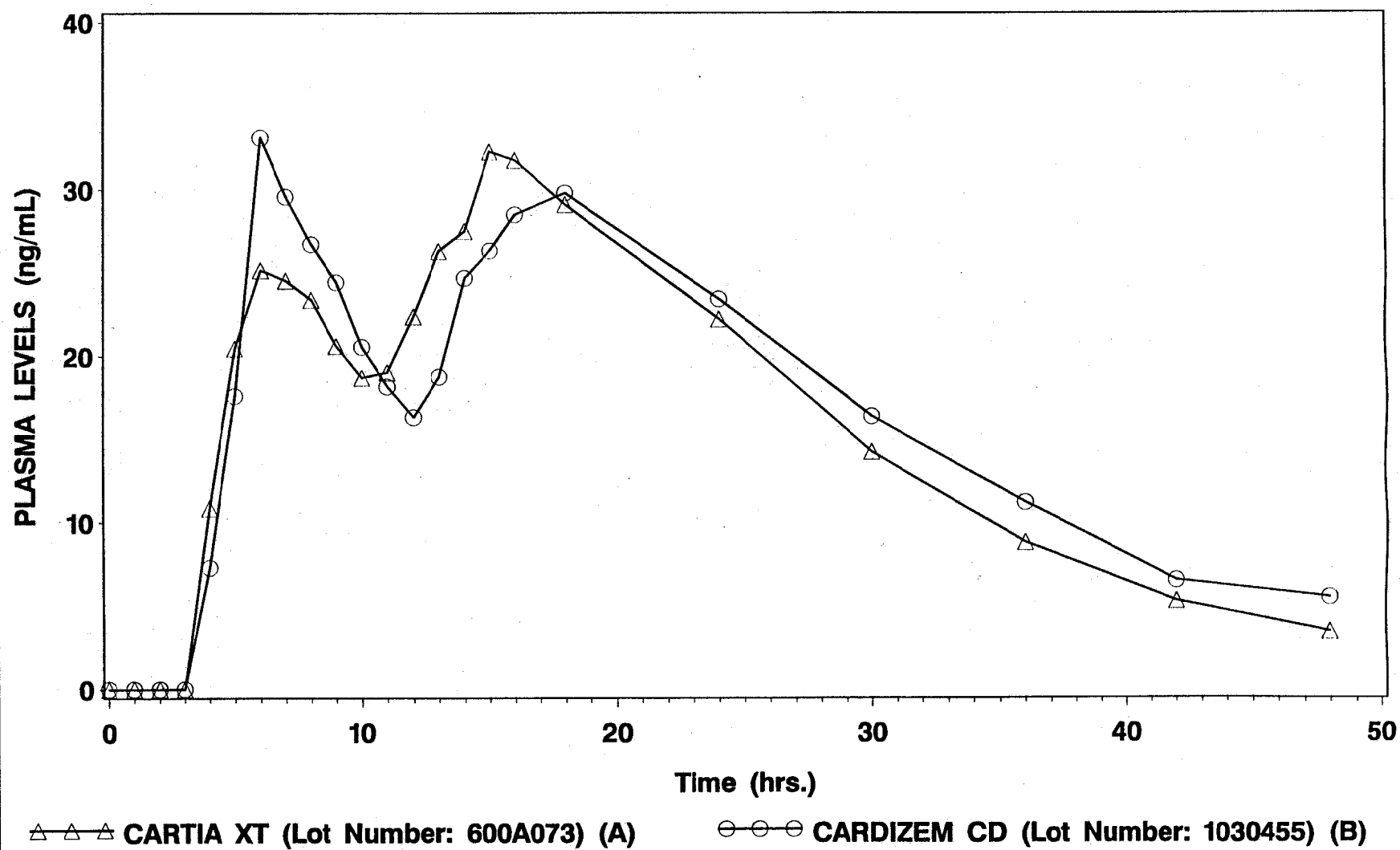


FIGURE 3.22

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 22

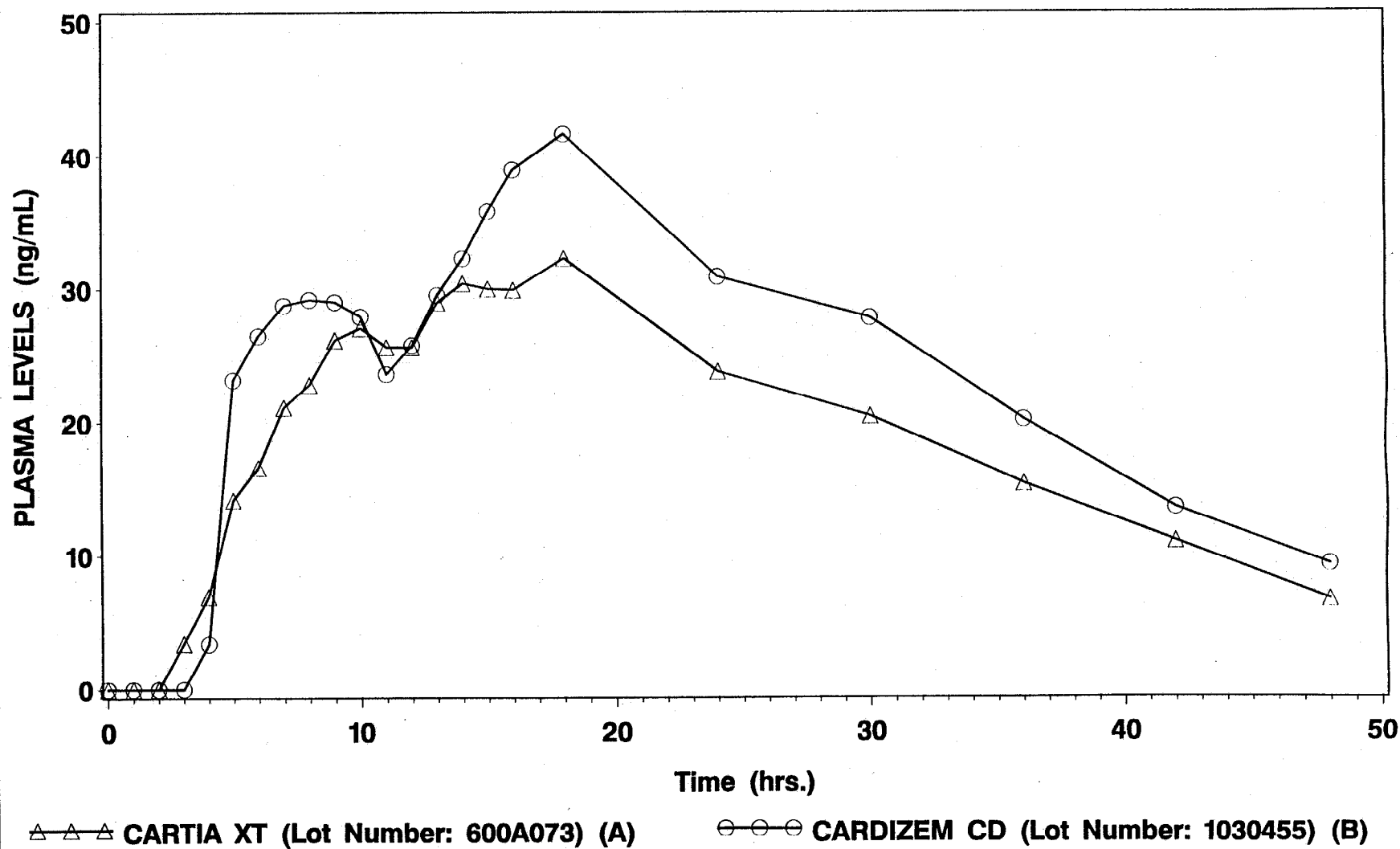
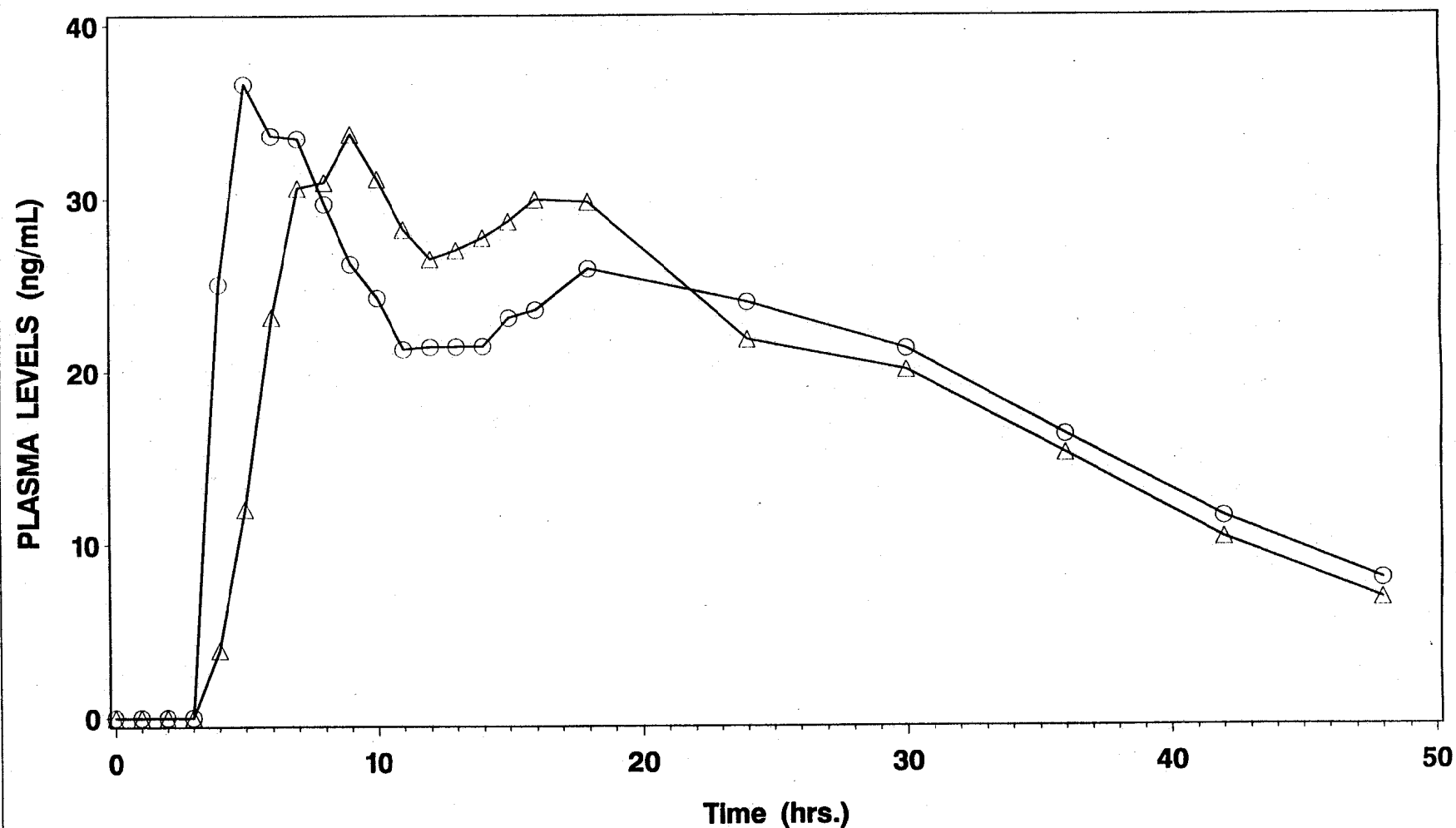


FIGURE 3.23

328

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 23



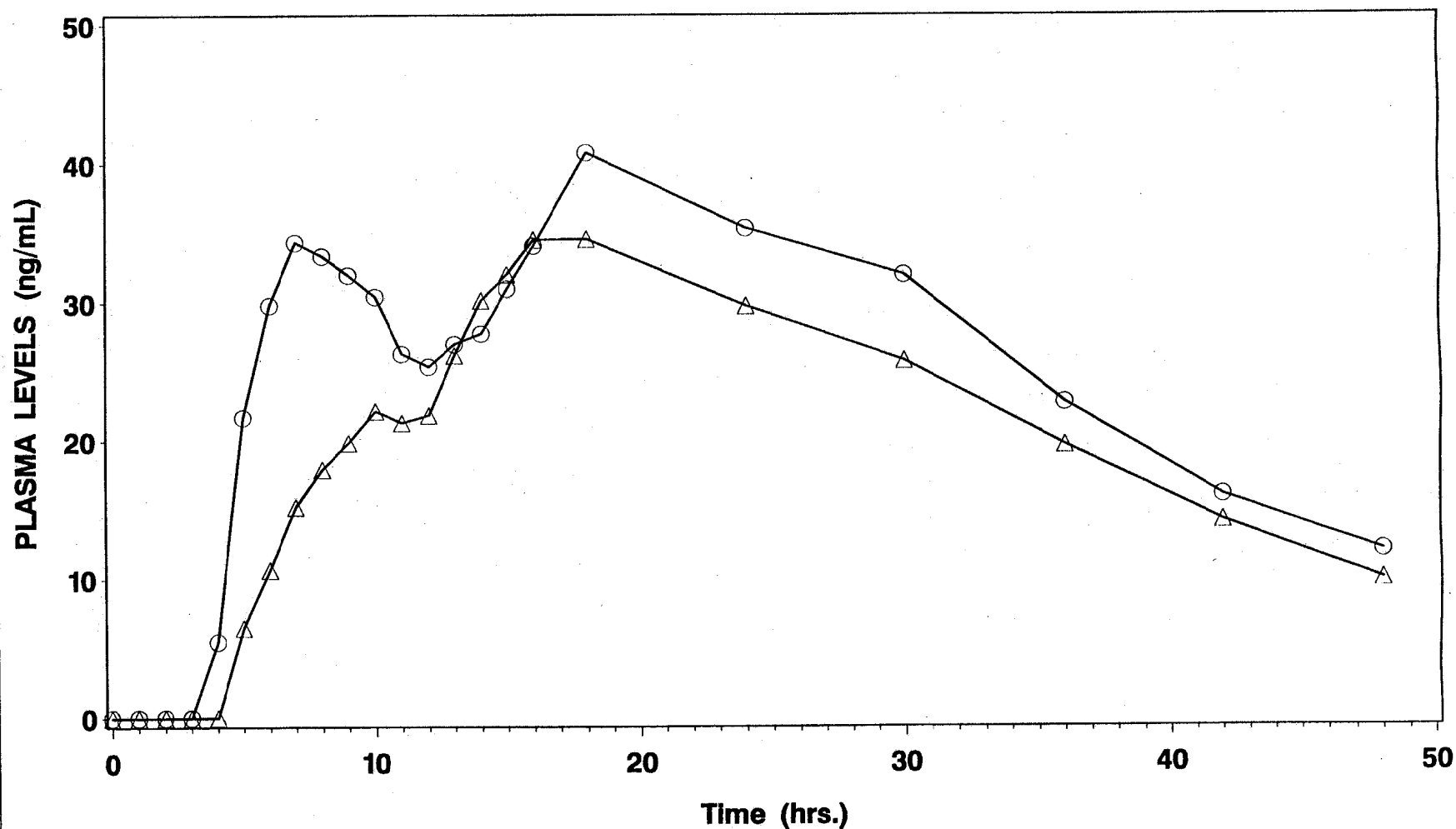
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.24

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 24



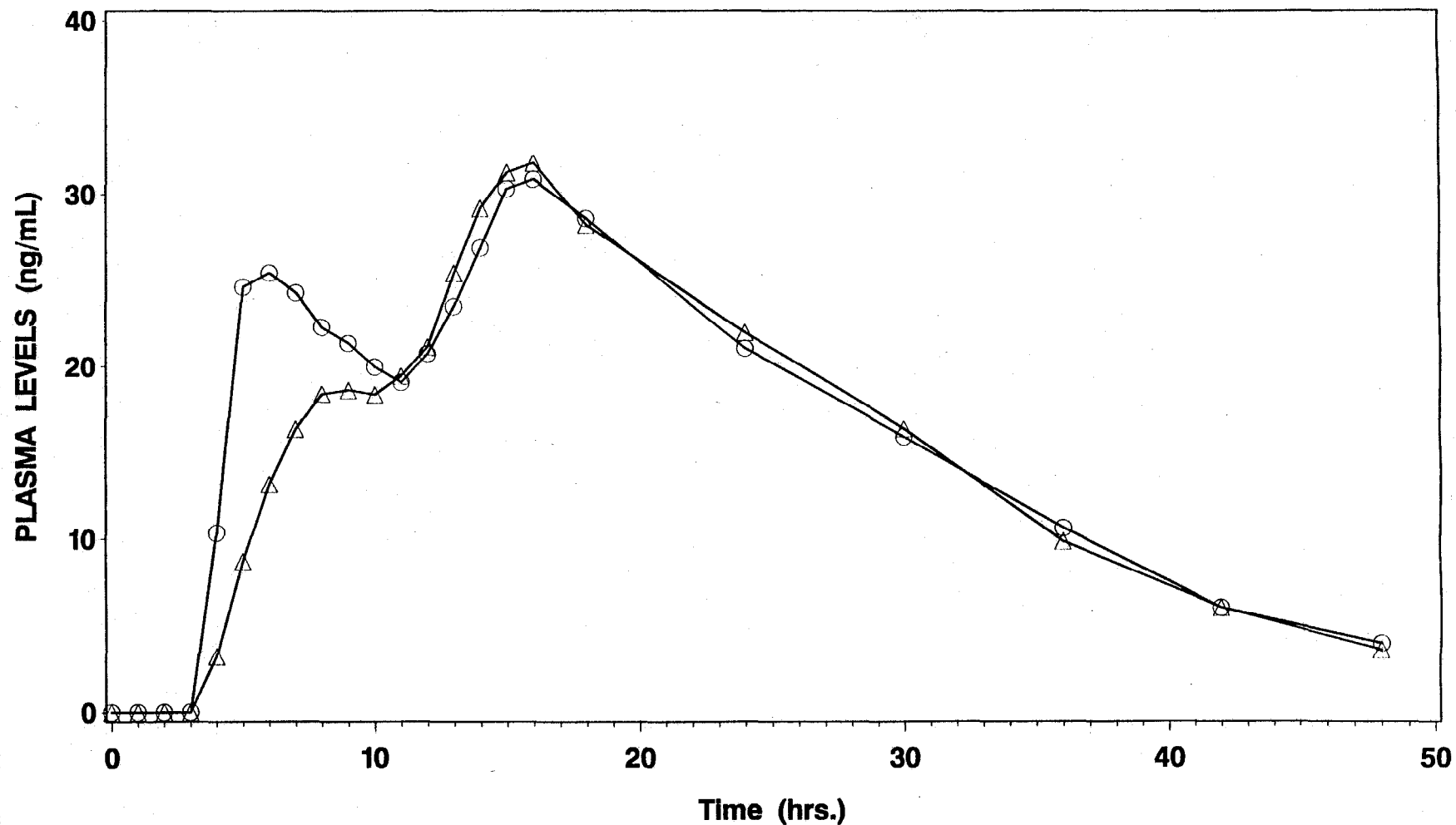
△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.25

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 25



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.26

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 26

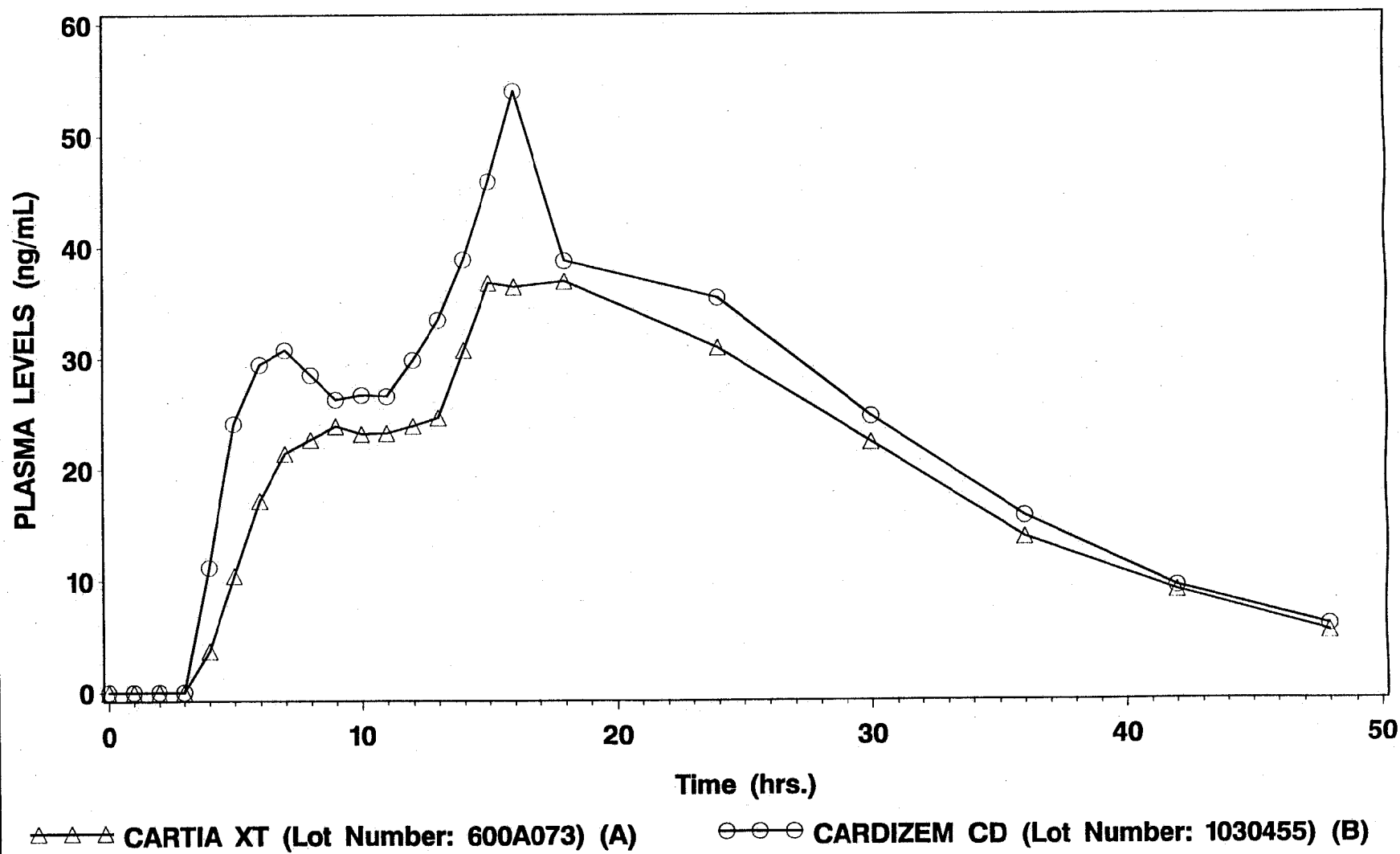
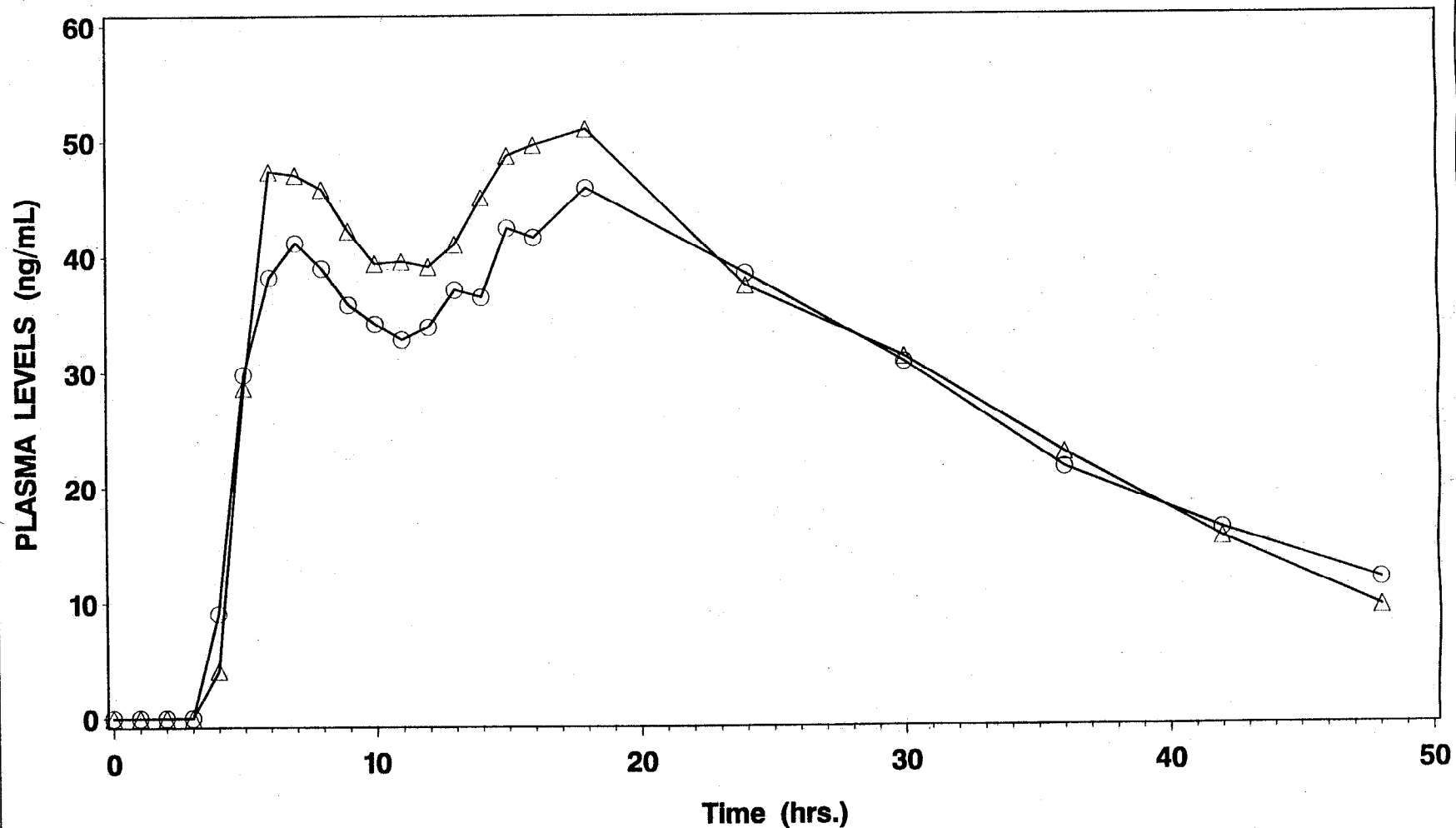


FIGURE 3.27

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 27



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

○-○-○ CARDIZEM CD (Lot Number: 1030455) (B)

FIGURE 3.28

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 28

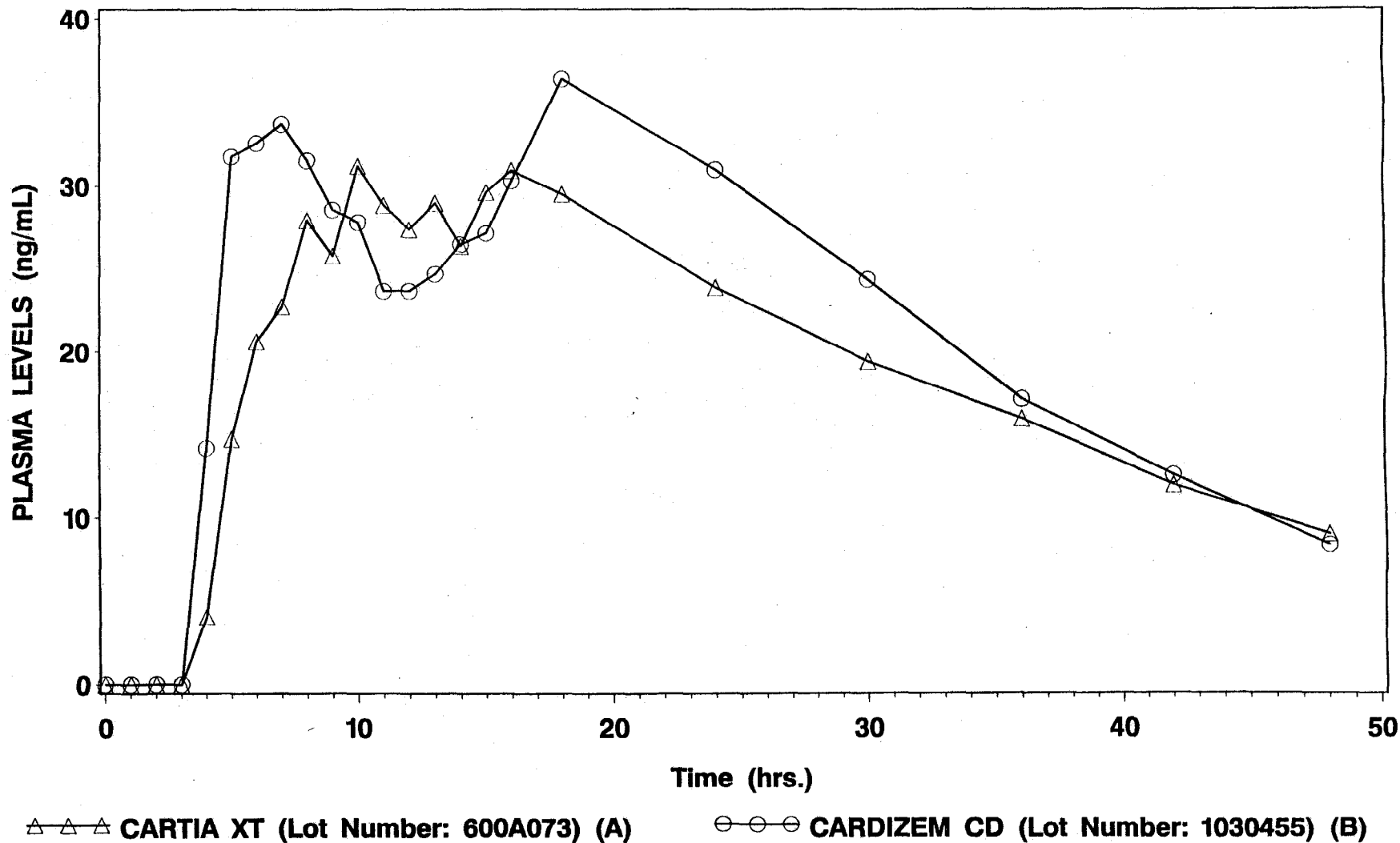
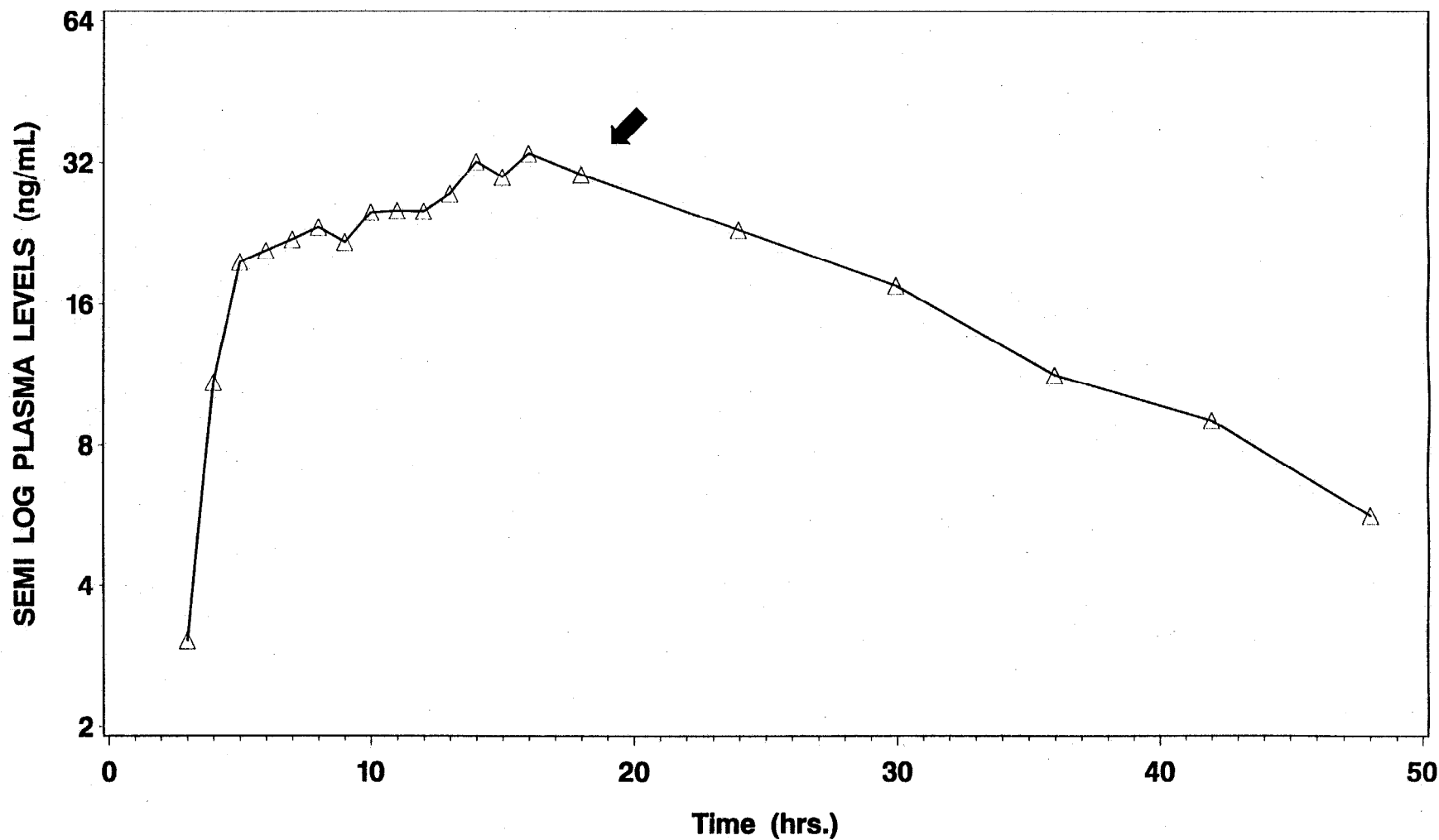


FIGURE 3.29

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 01



△-△-△ **CARTIA XT (Lot Number: 600A073) (A)**

FIGURE 3.30

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 03

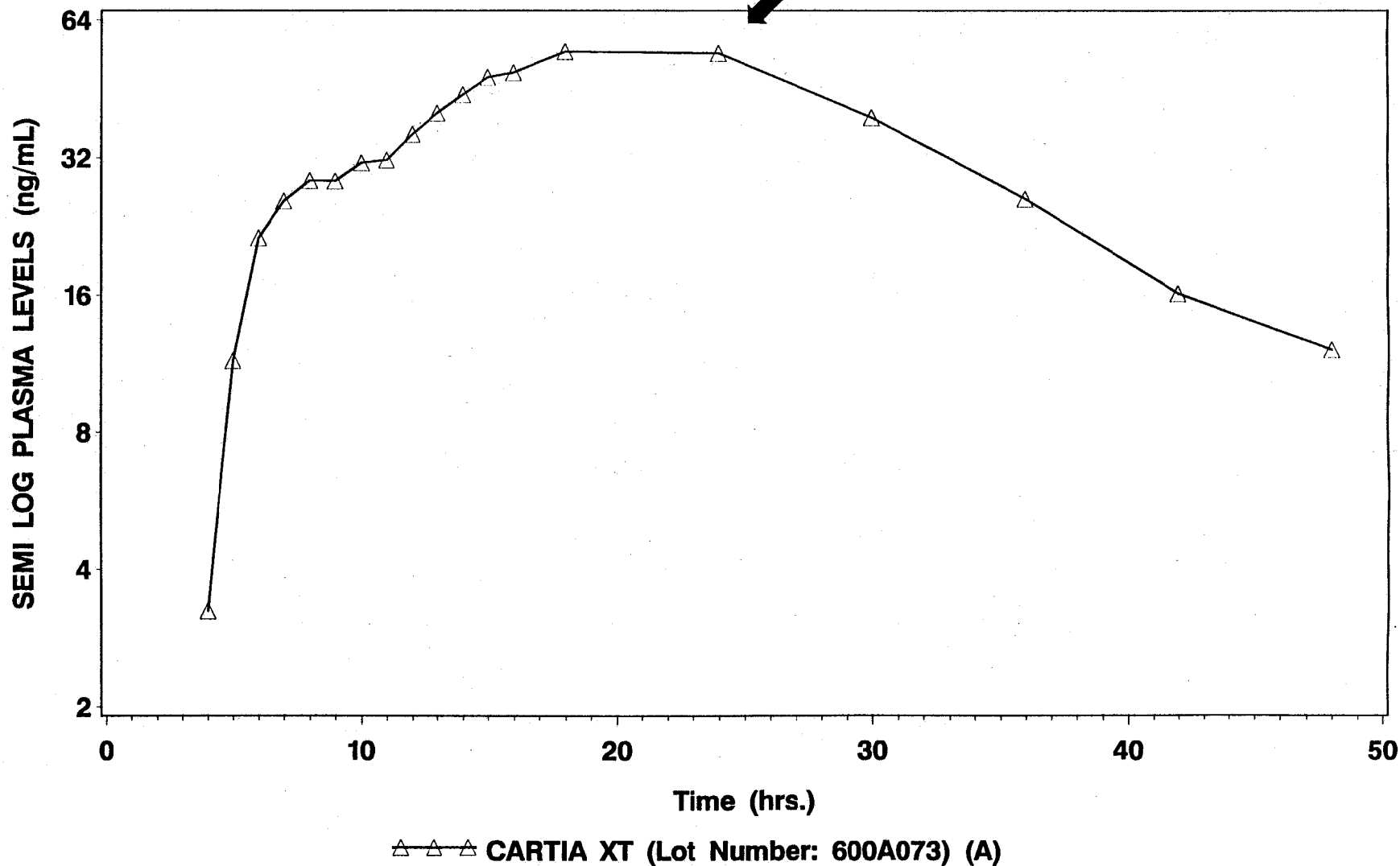


FIGURE 3.31

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 04

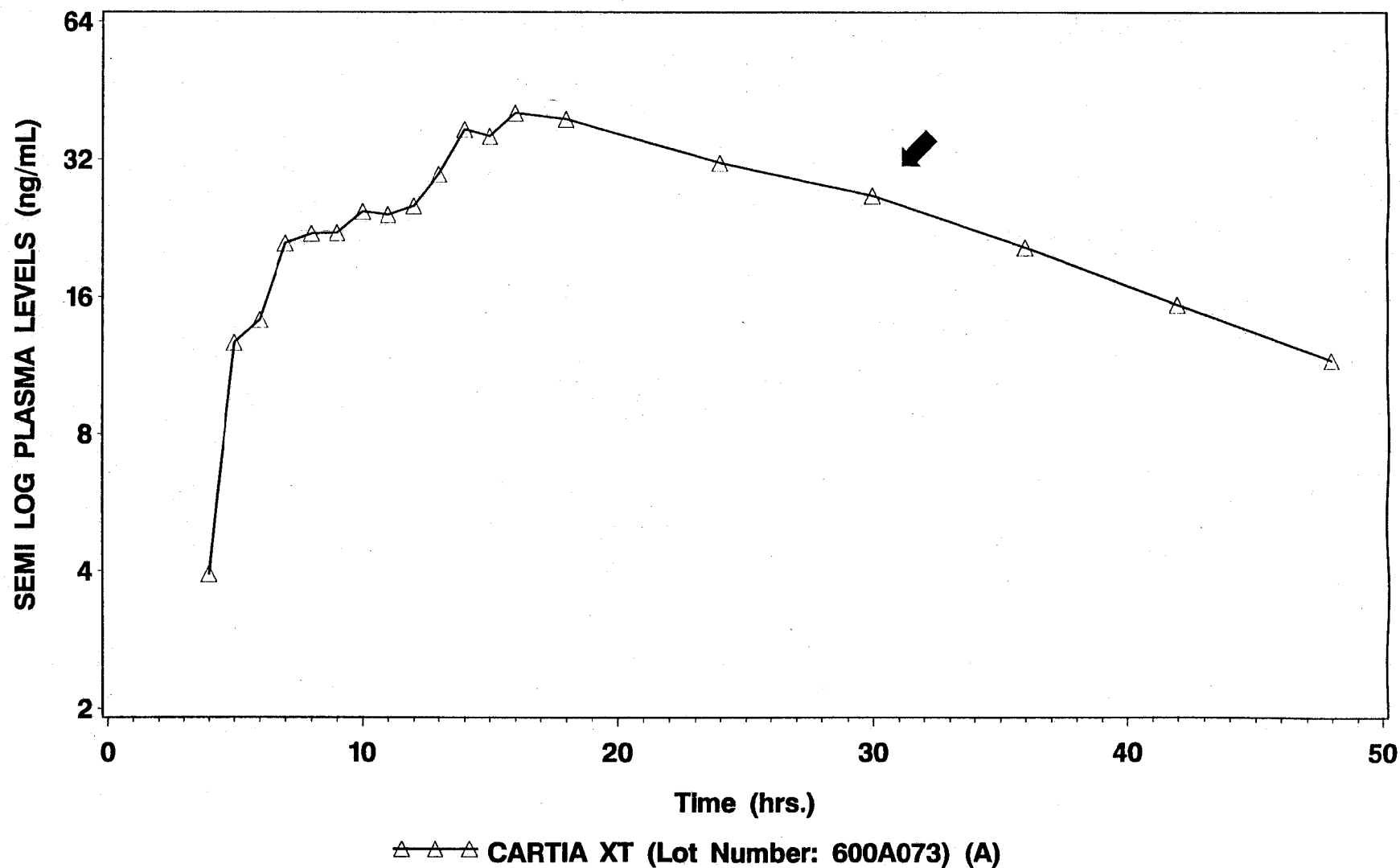


FIGURE 3.32

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 05

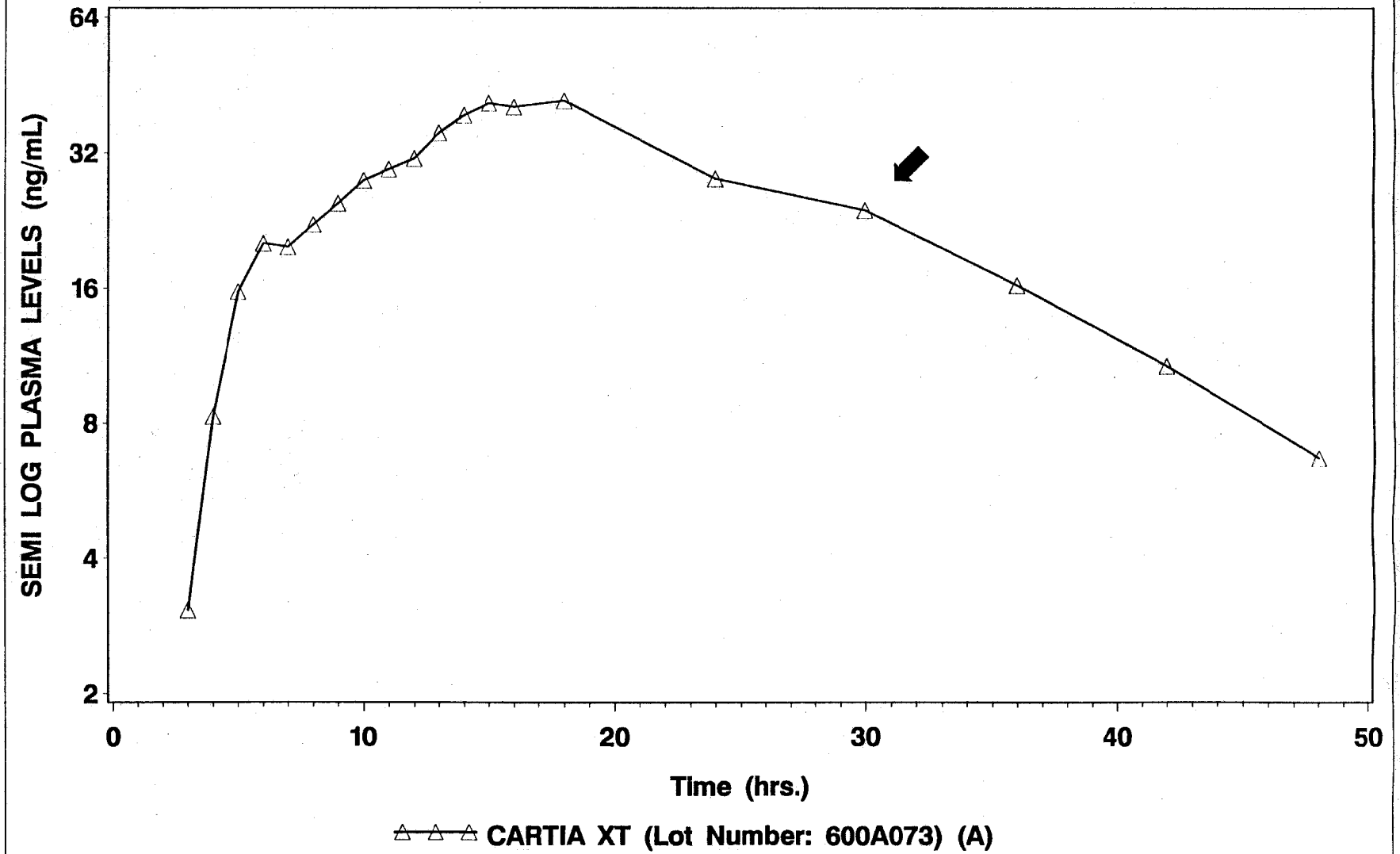


FIGURE 3.33

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 06

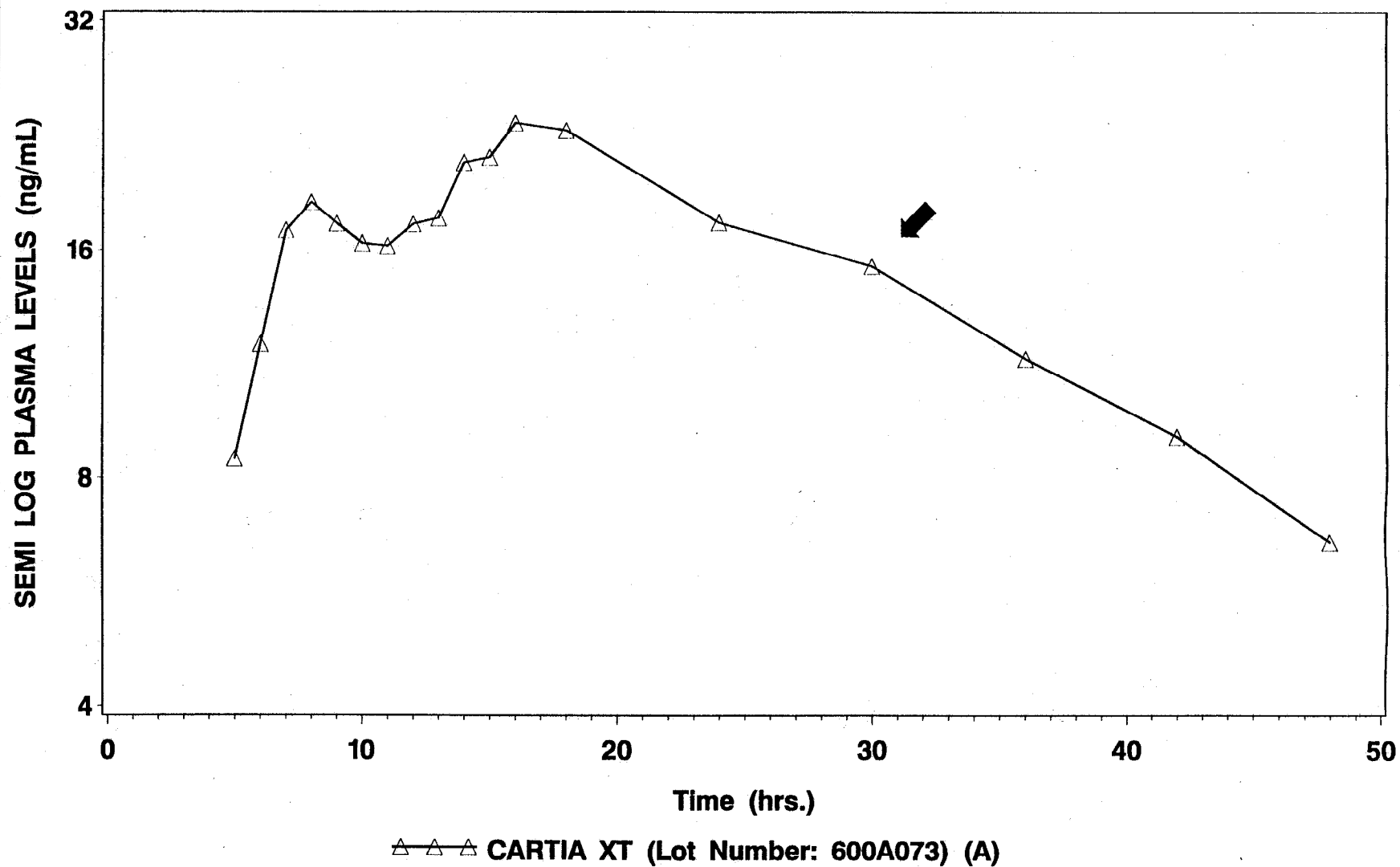
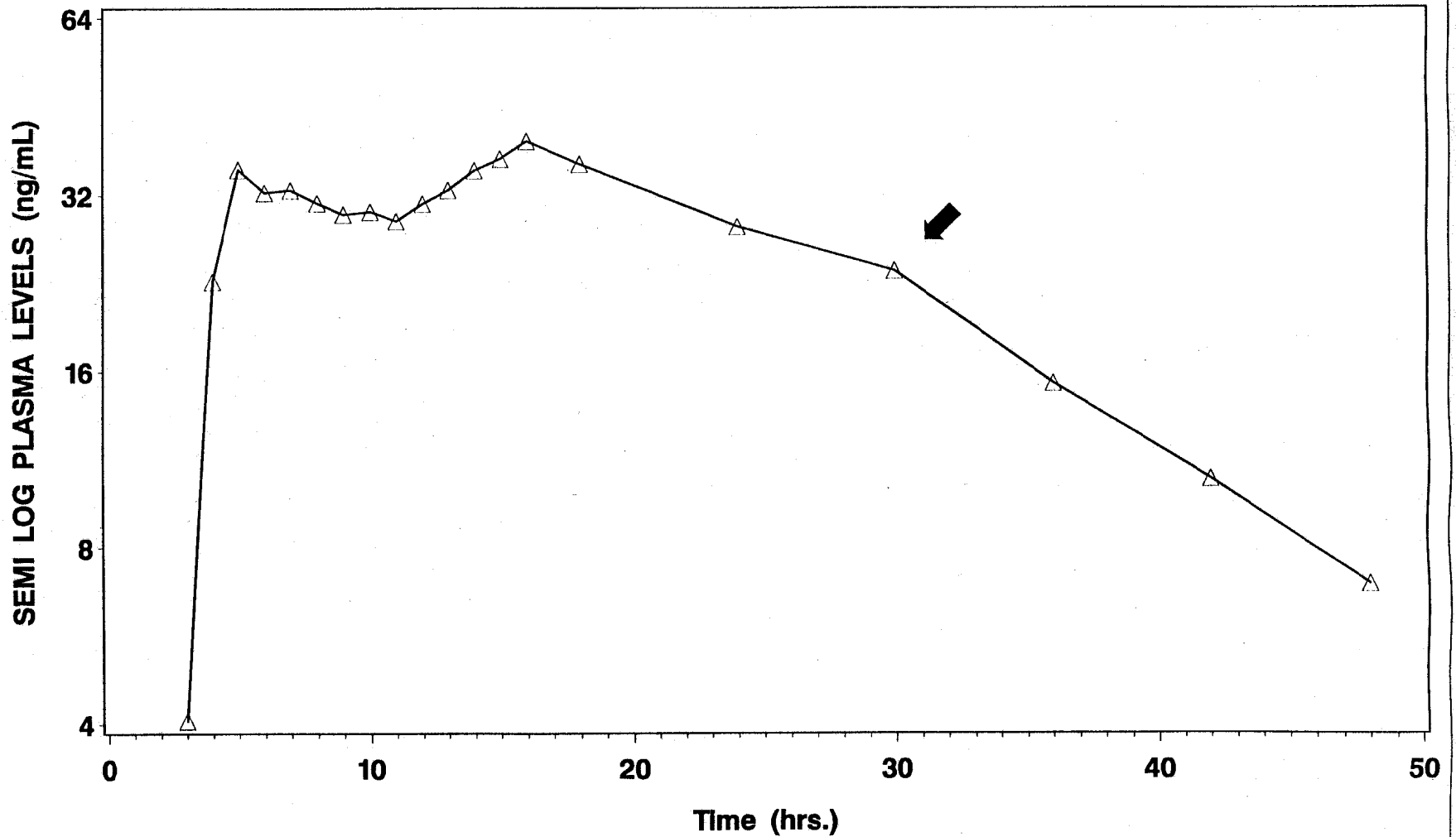


FIGURE 3.34

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 07

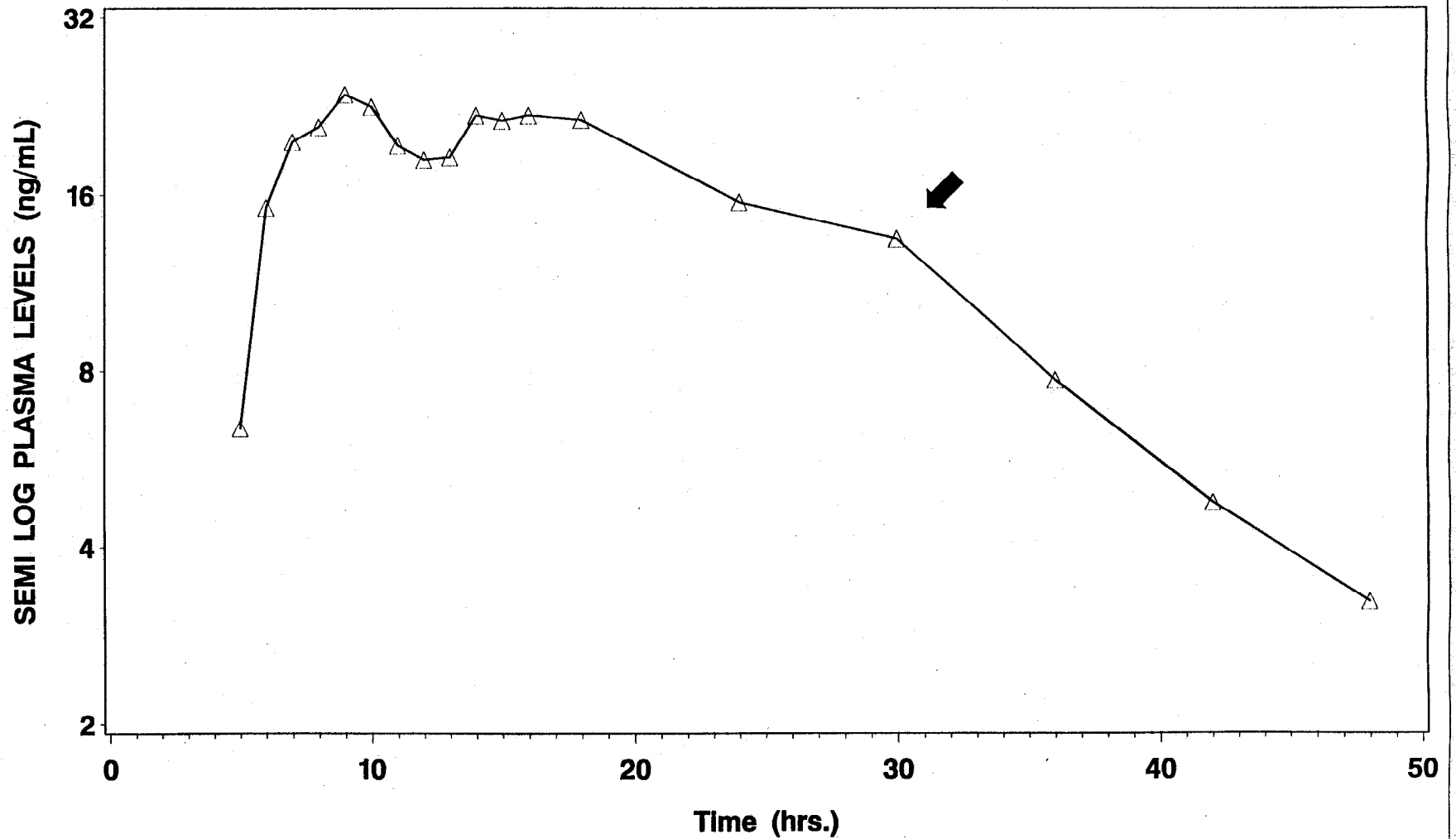


△△△ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 3.35

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 08



—△—△—△ **CARTIA XT (Lot Number: 600A073) (A)**

FIGURE 3.36

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 09

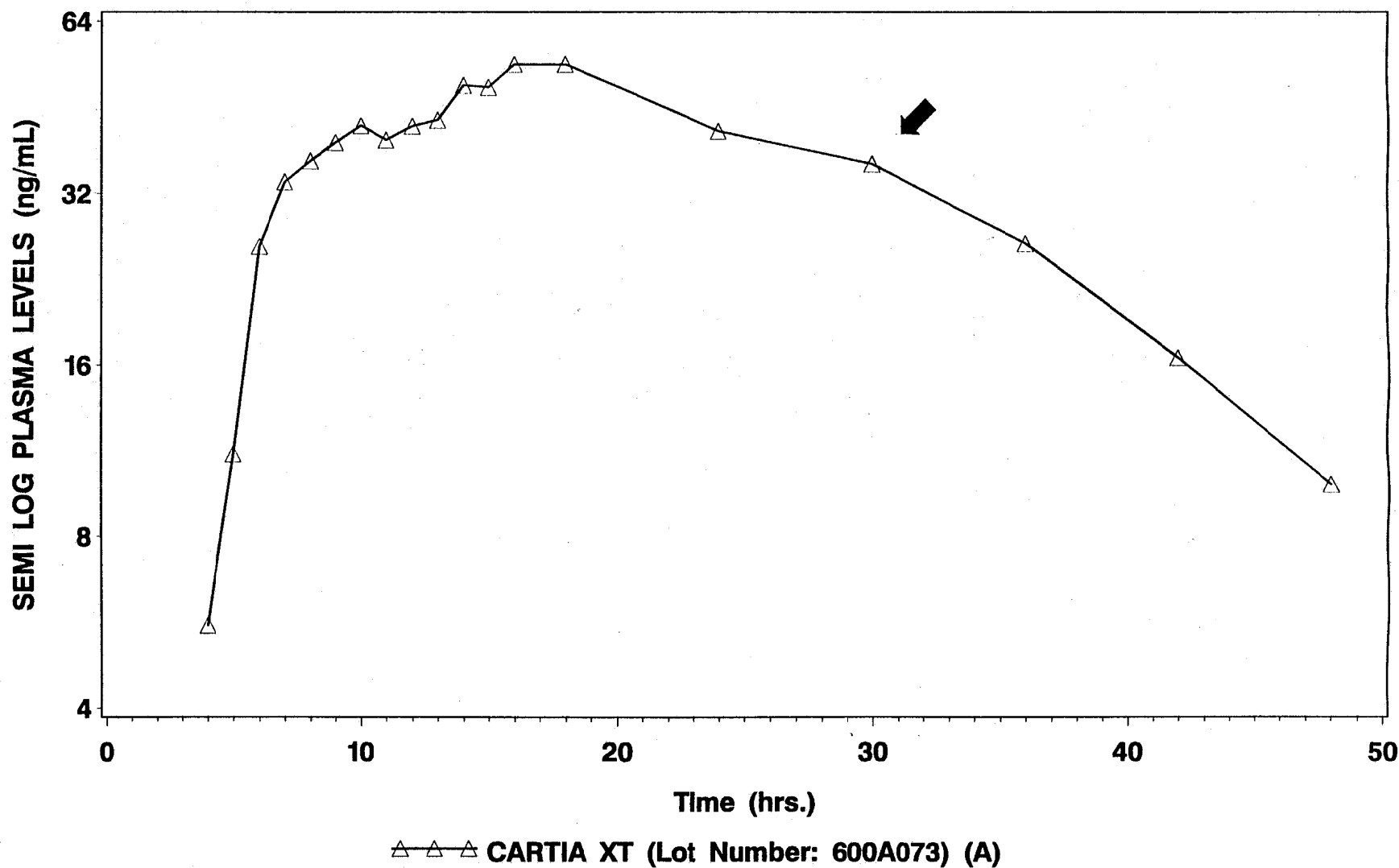


FIGURE 3.37

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 10

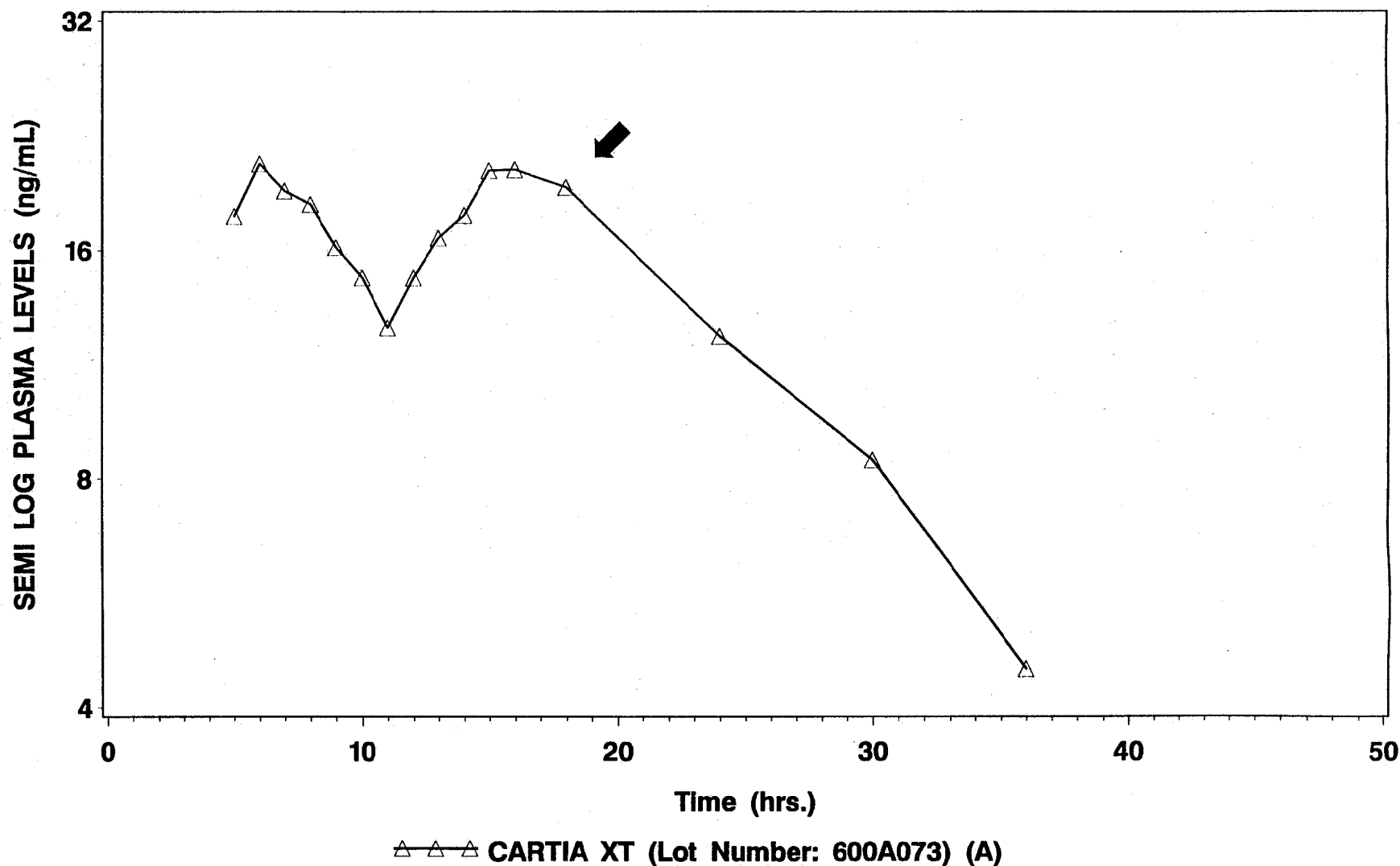


FIGURE 3.38

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 11

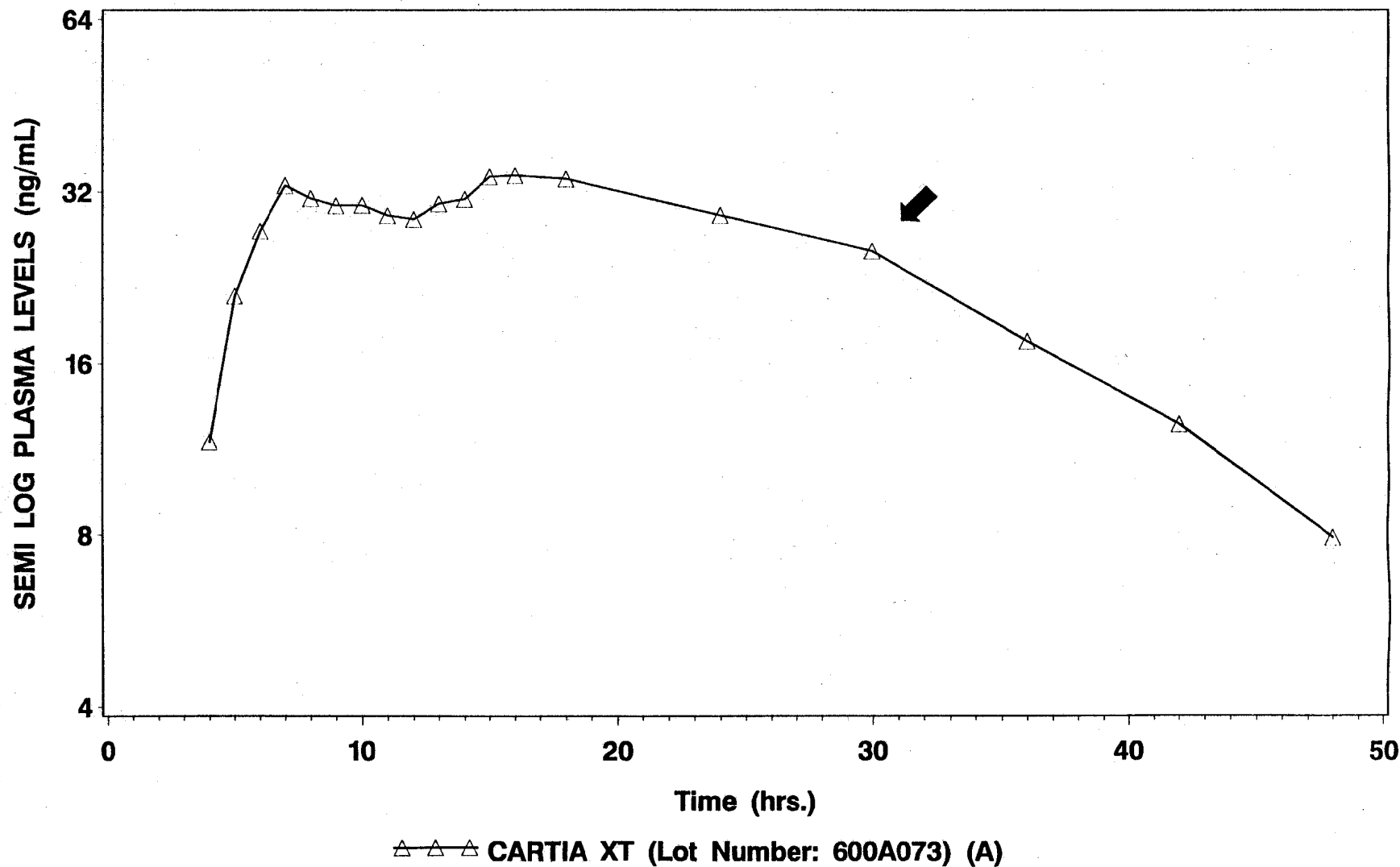


FIGURE 3.39

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 12

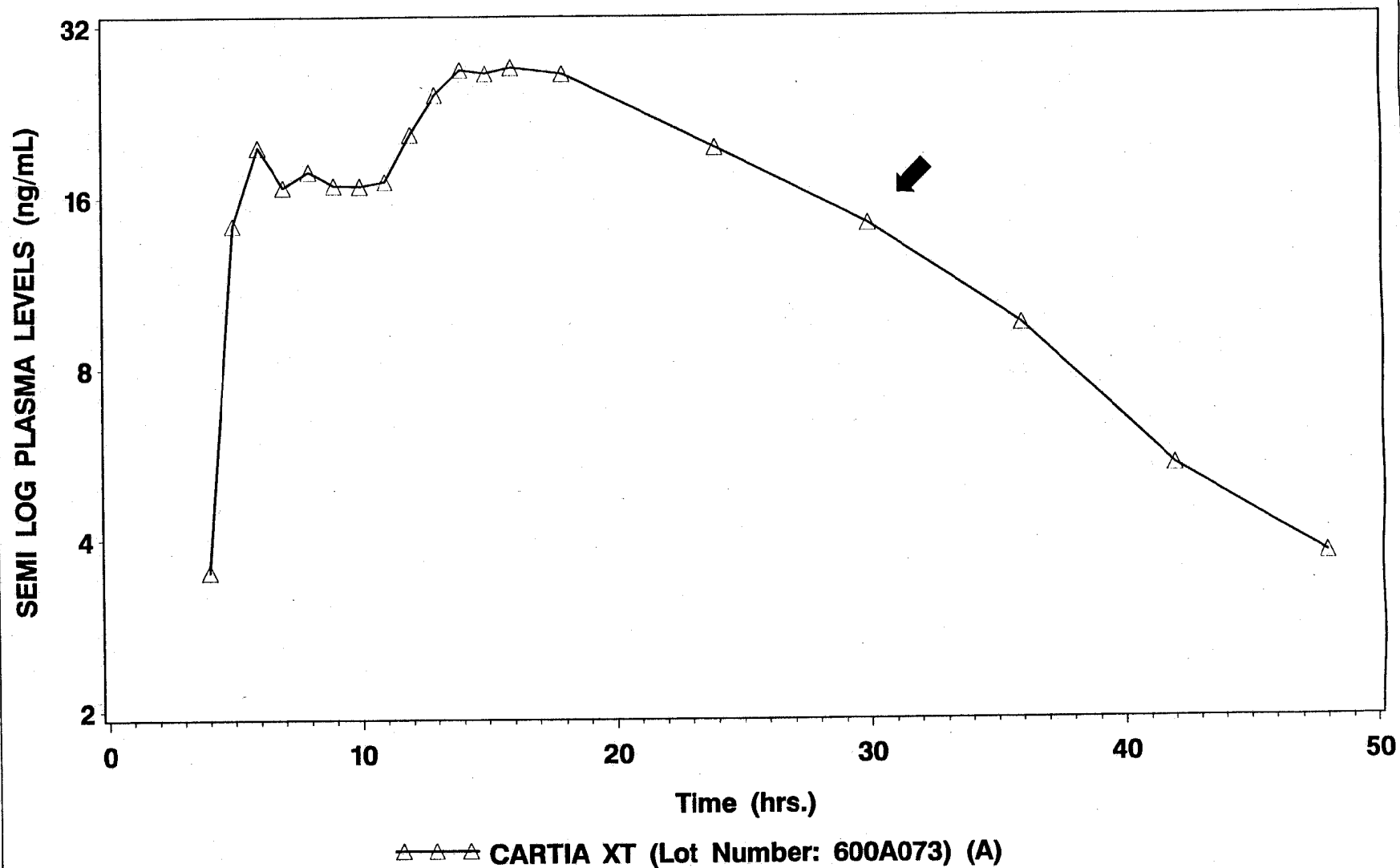
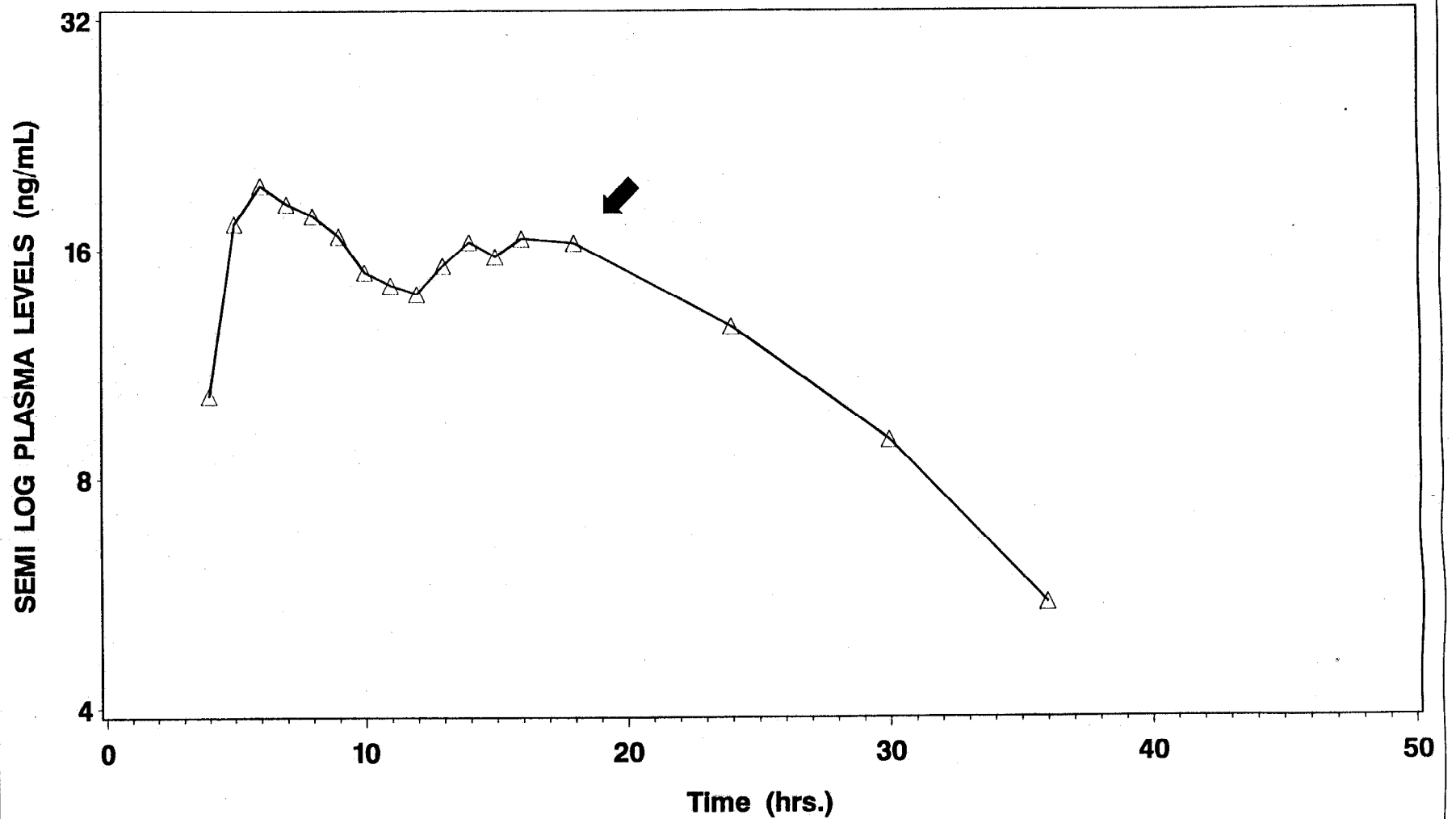


FIGURE 3.40

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 13

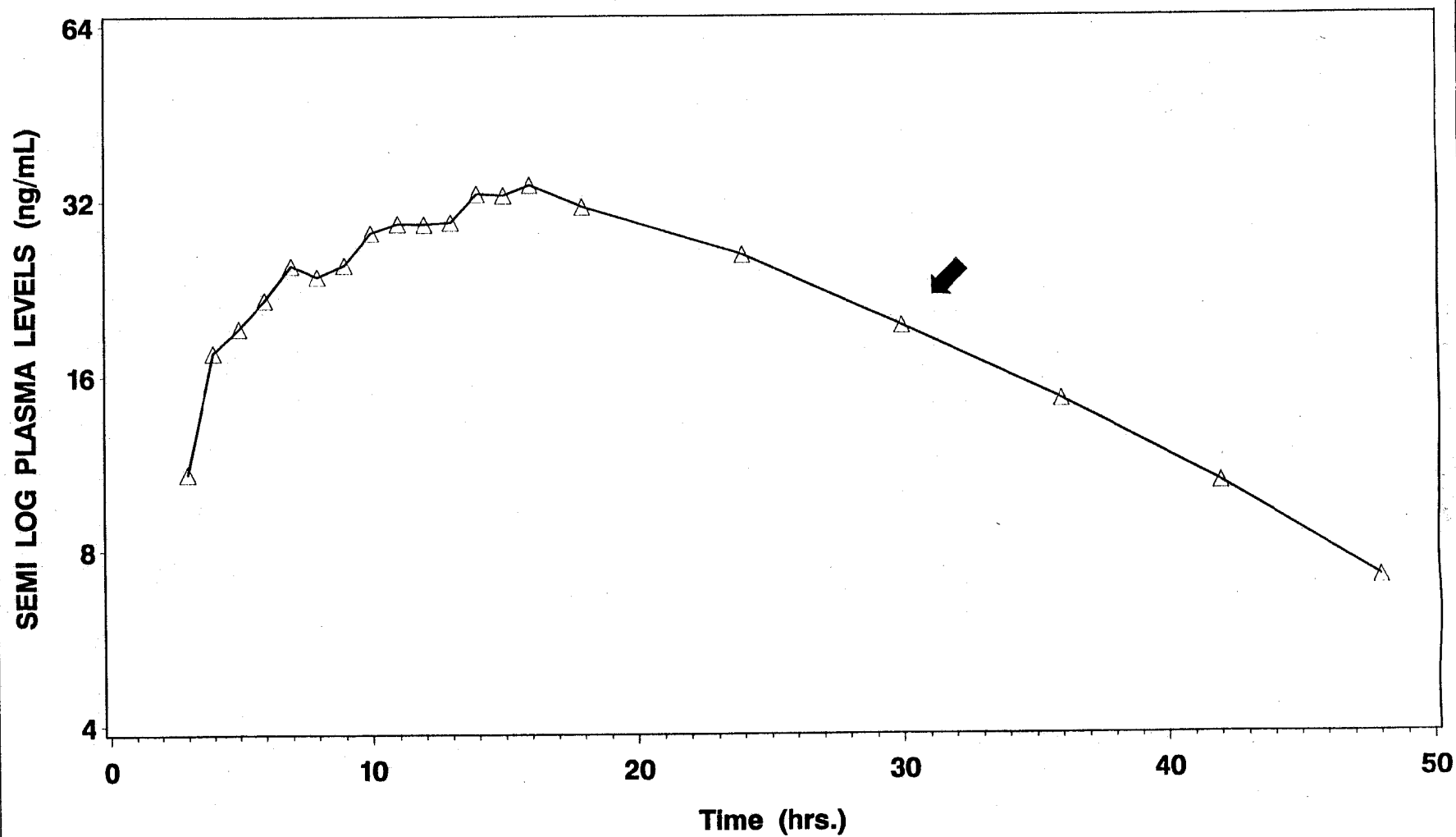


△-△-△ **CARTIA XT (Lot Number: 600A073) (A)**

FIGURE 3.41

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

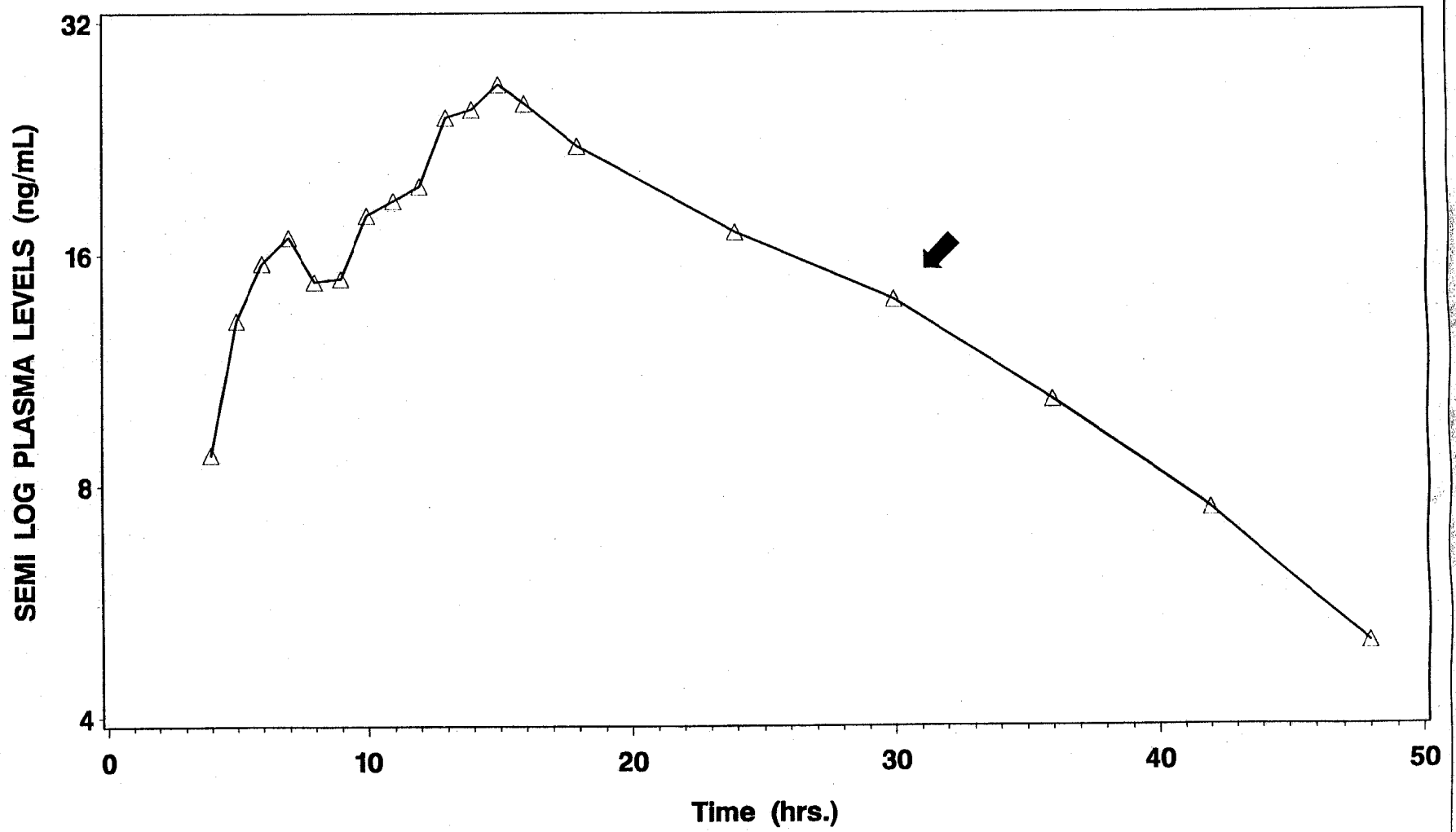
SUBJECT = 14



△-△-△ **CARTIA XT (Lot Number: 600A073) (A)**

FIGURE 3.42

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 15

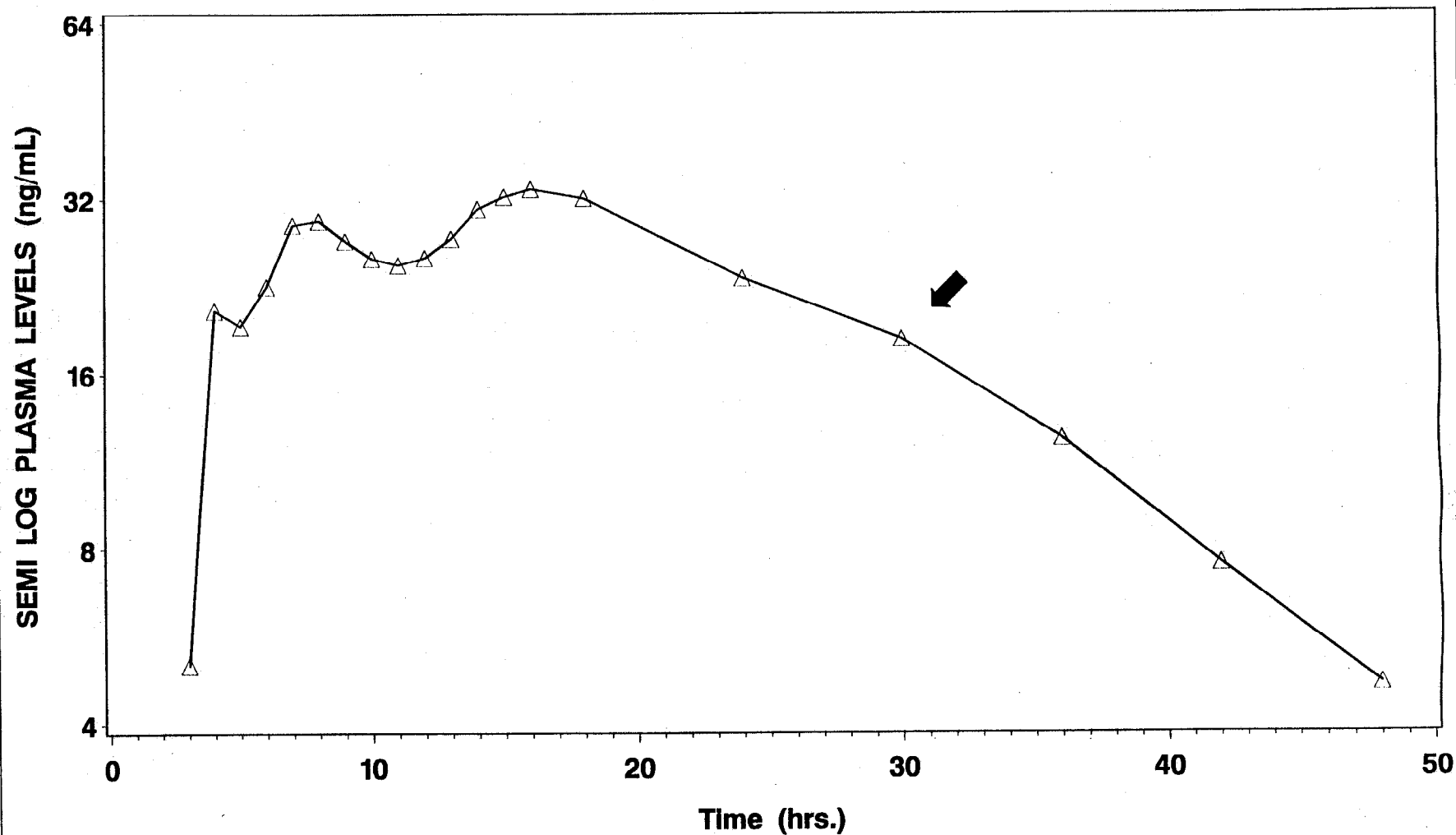


△-△-△ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 3.43

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 16



△ — △ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 3.44

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 17

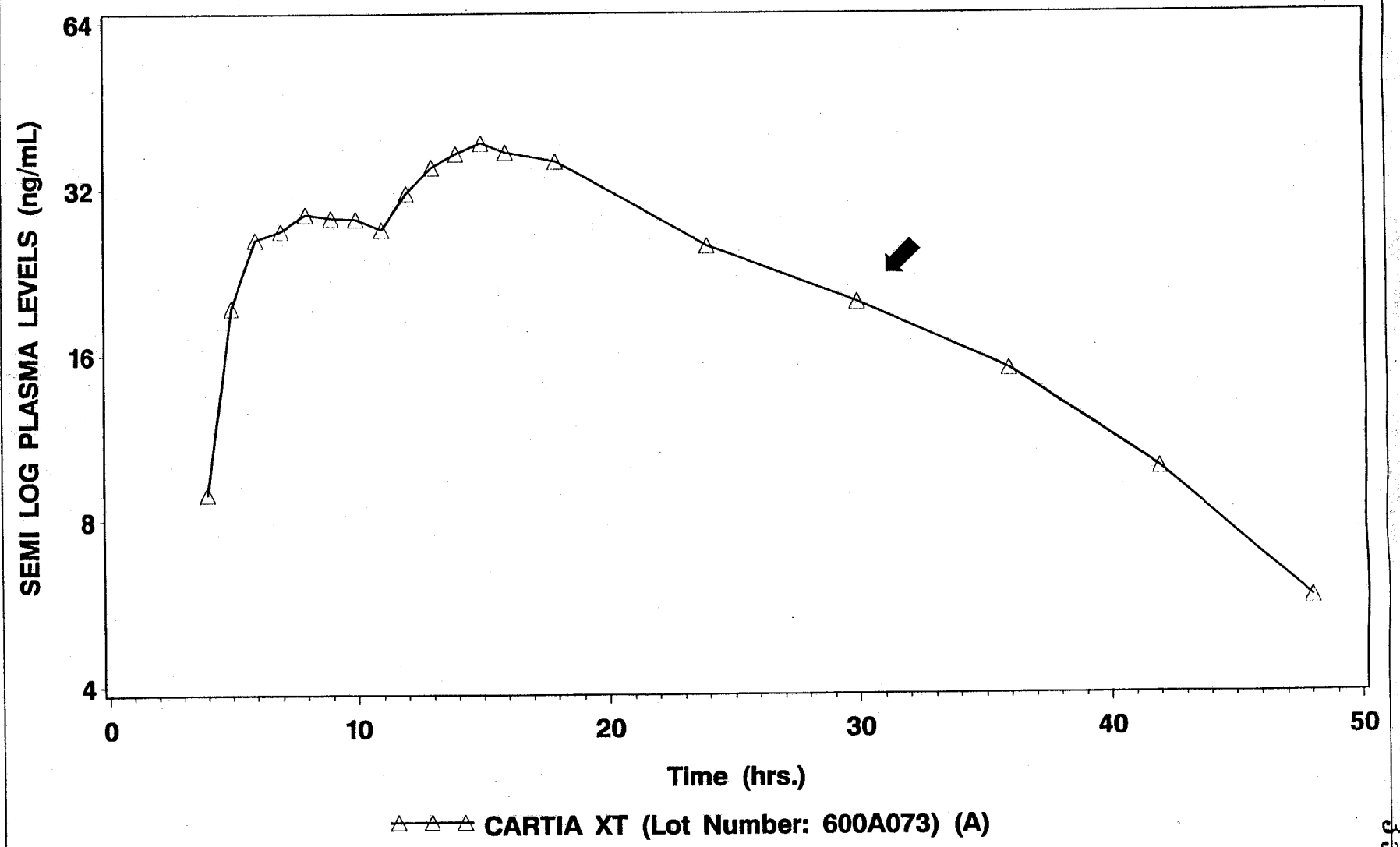
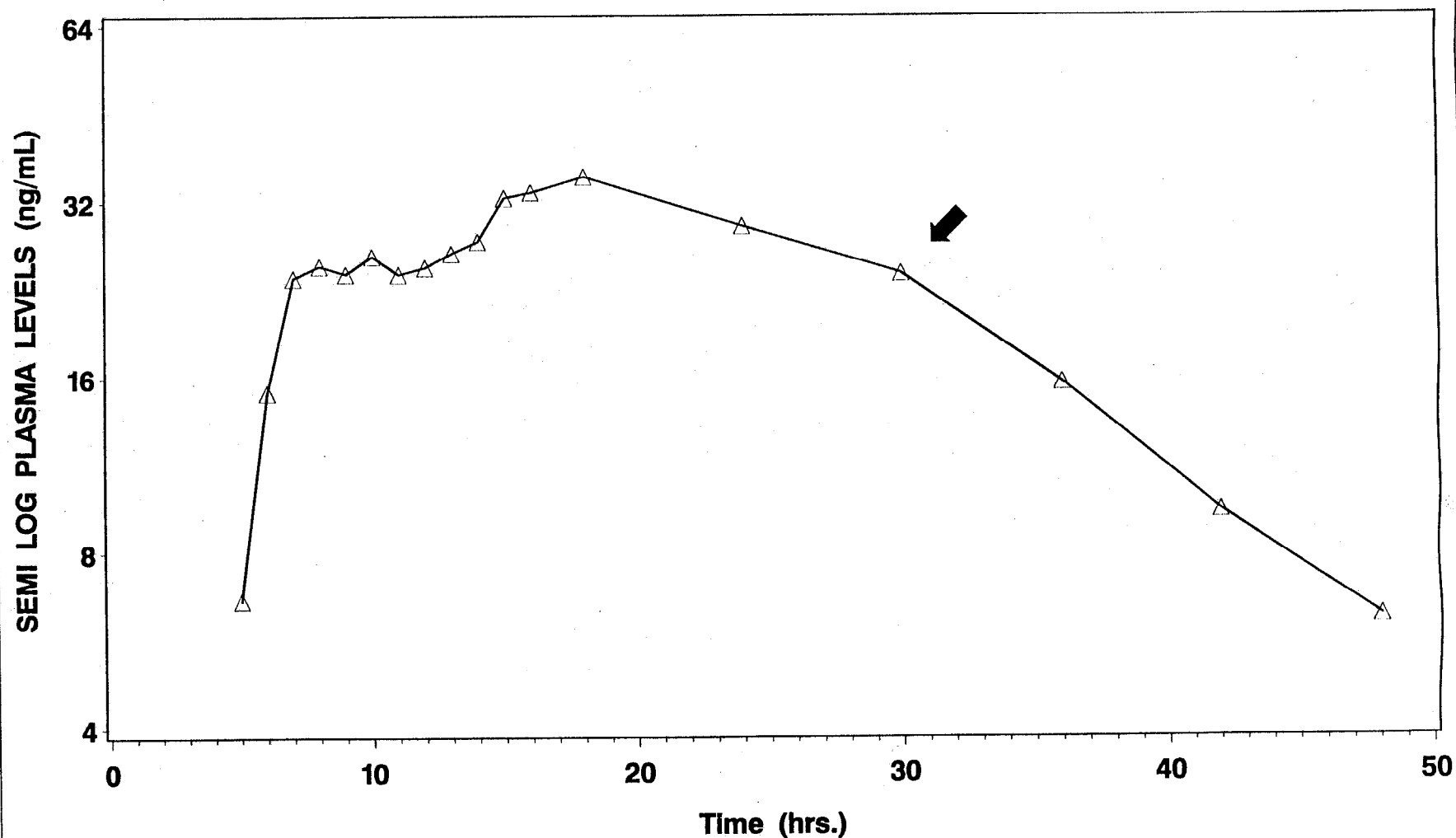


FIGURE 3.45

037

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 18



△-△-△ CARTIA XT (Lot Number: 600A073) (A)

FIGURE 3.46

321

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 19

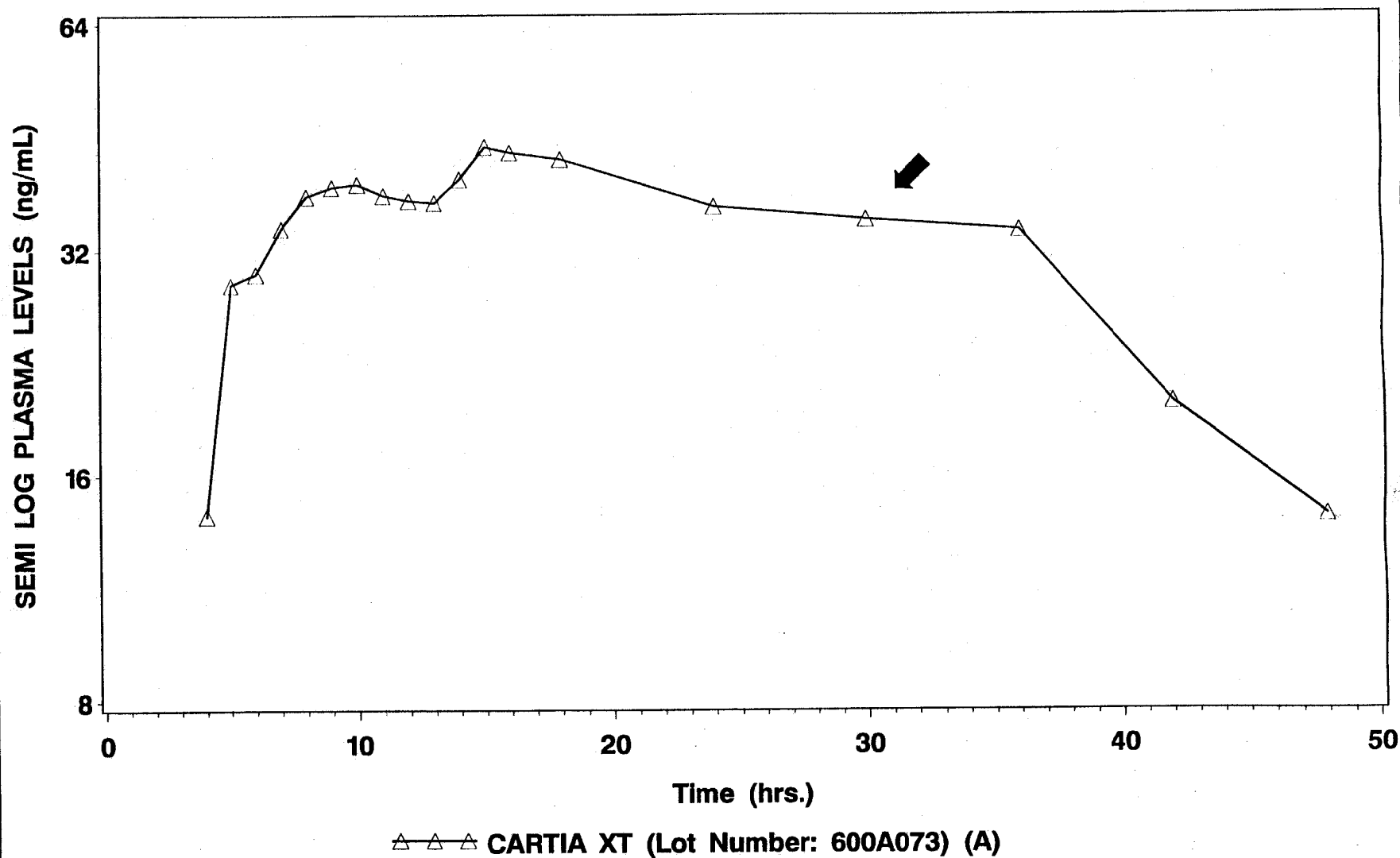
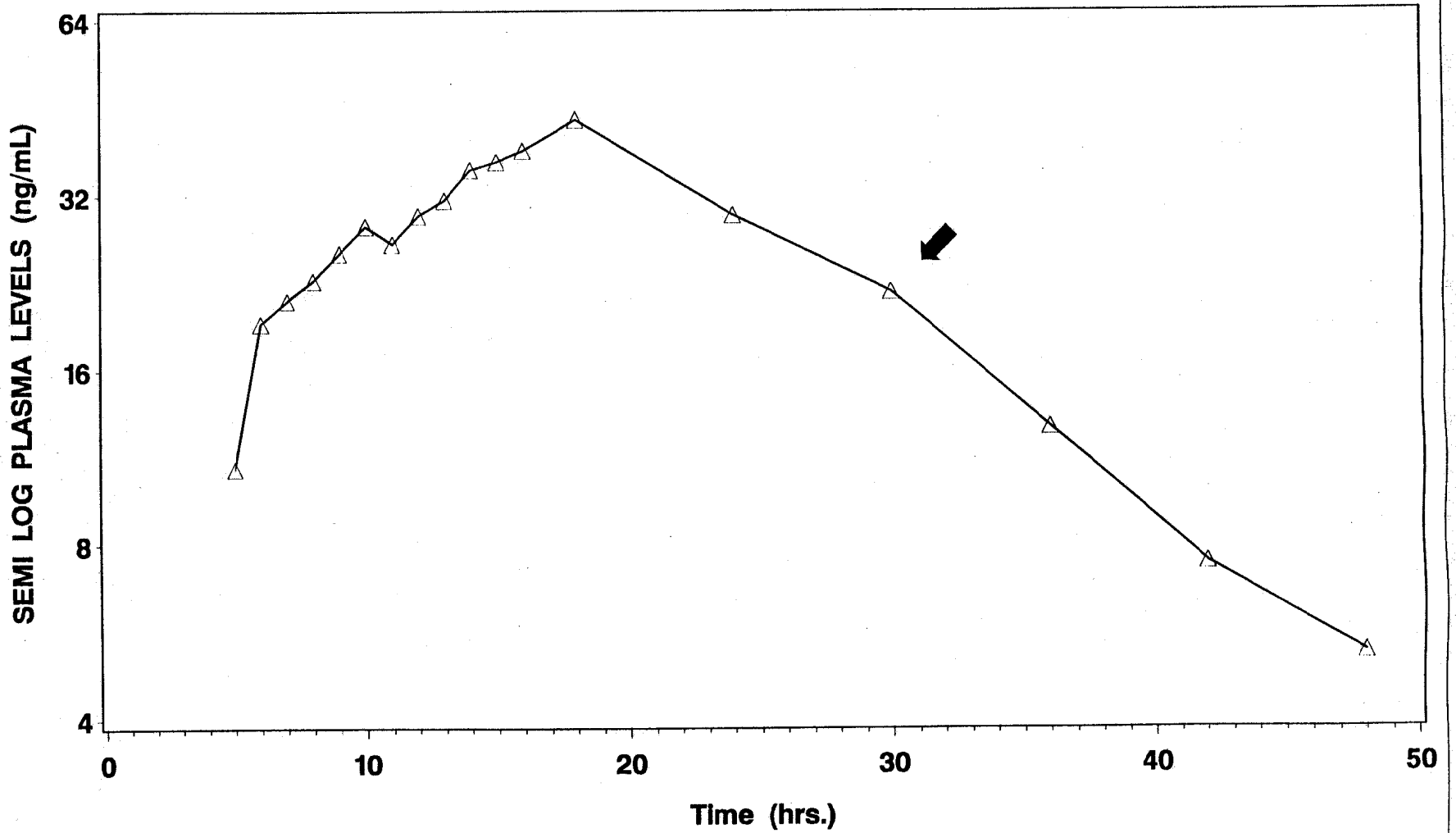


FIGURE 3.47

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 20

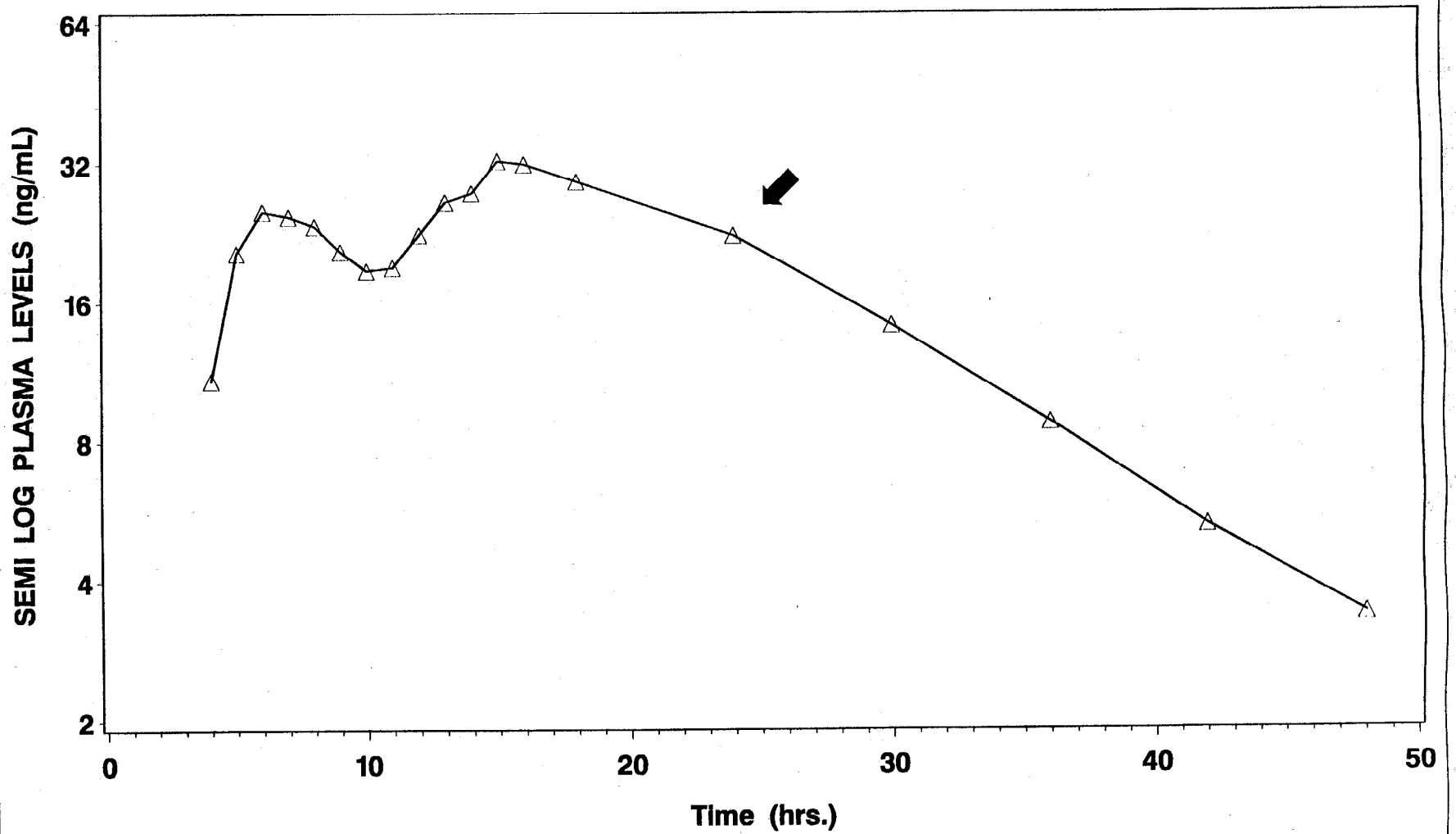


—△—△—△ **CARTIA XT (Lot Number: 600A073) (A)**

FIGURE 3.48

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 21



△ — △ — △ **CARTIA XT (Lot Number: 600A073) (A)**

FIGURE 3.49

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 22

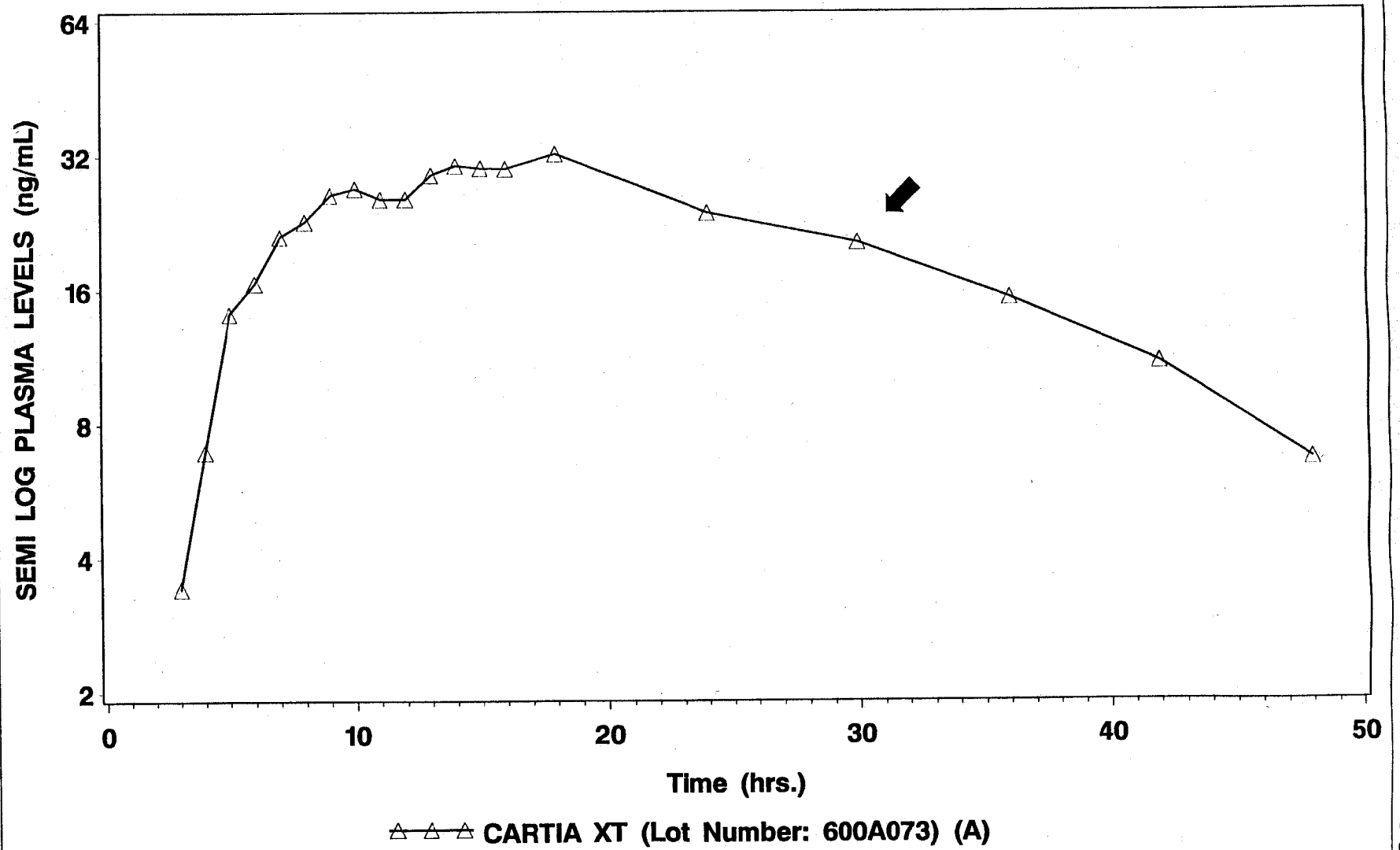
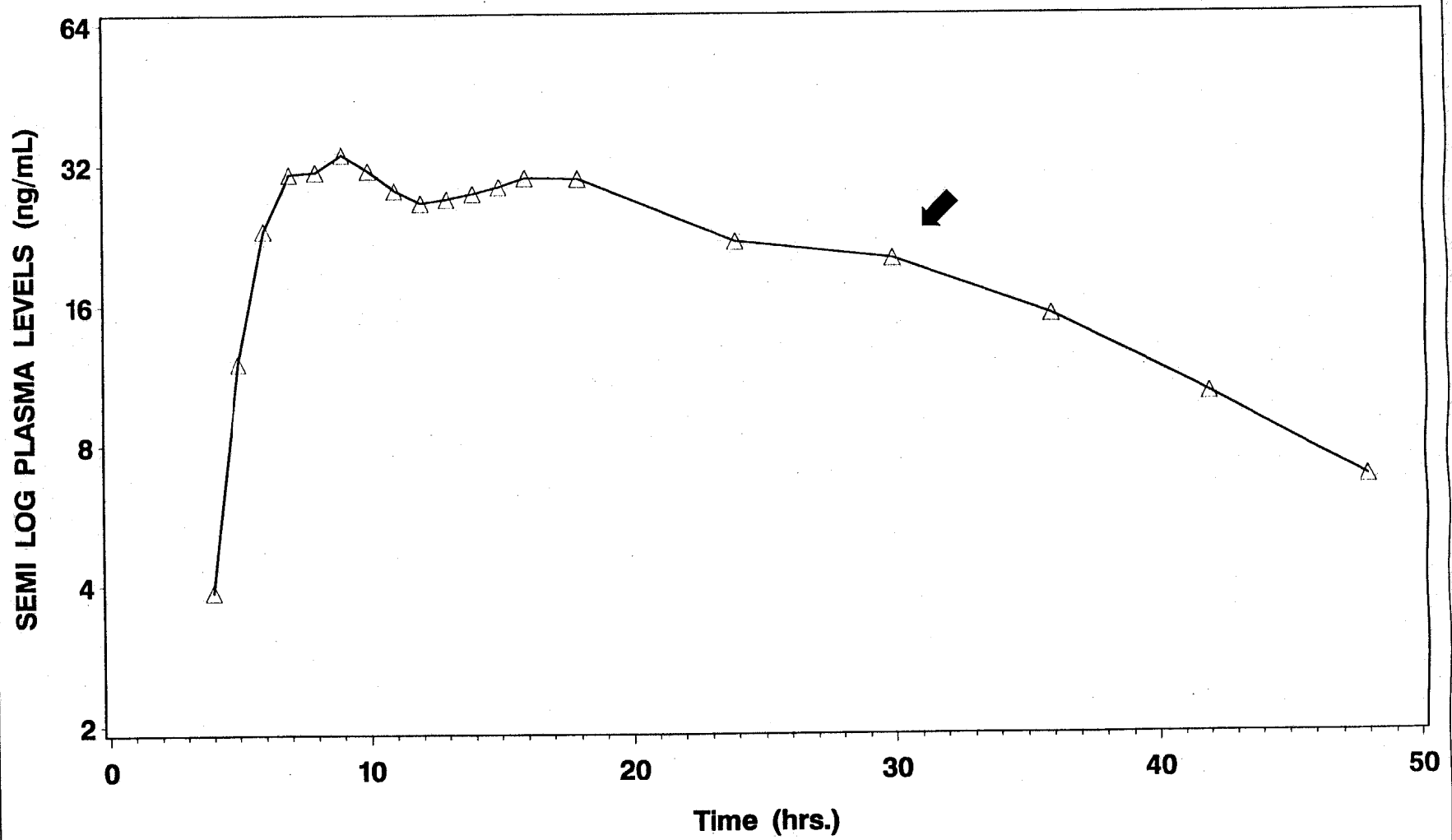


FIGURE 3.50

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 23



△—△—△ **CARTIA XT (Lot Number: 600A073) (A)**

FIGURE 3.51

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 24

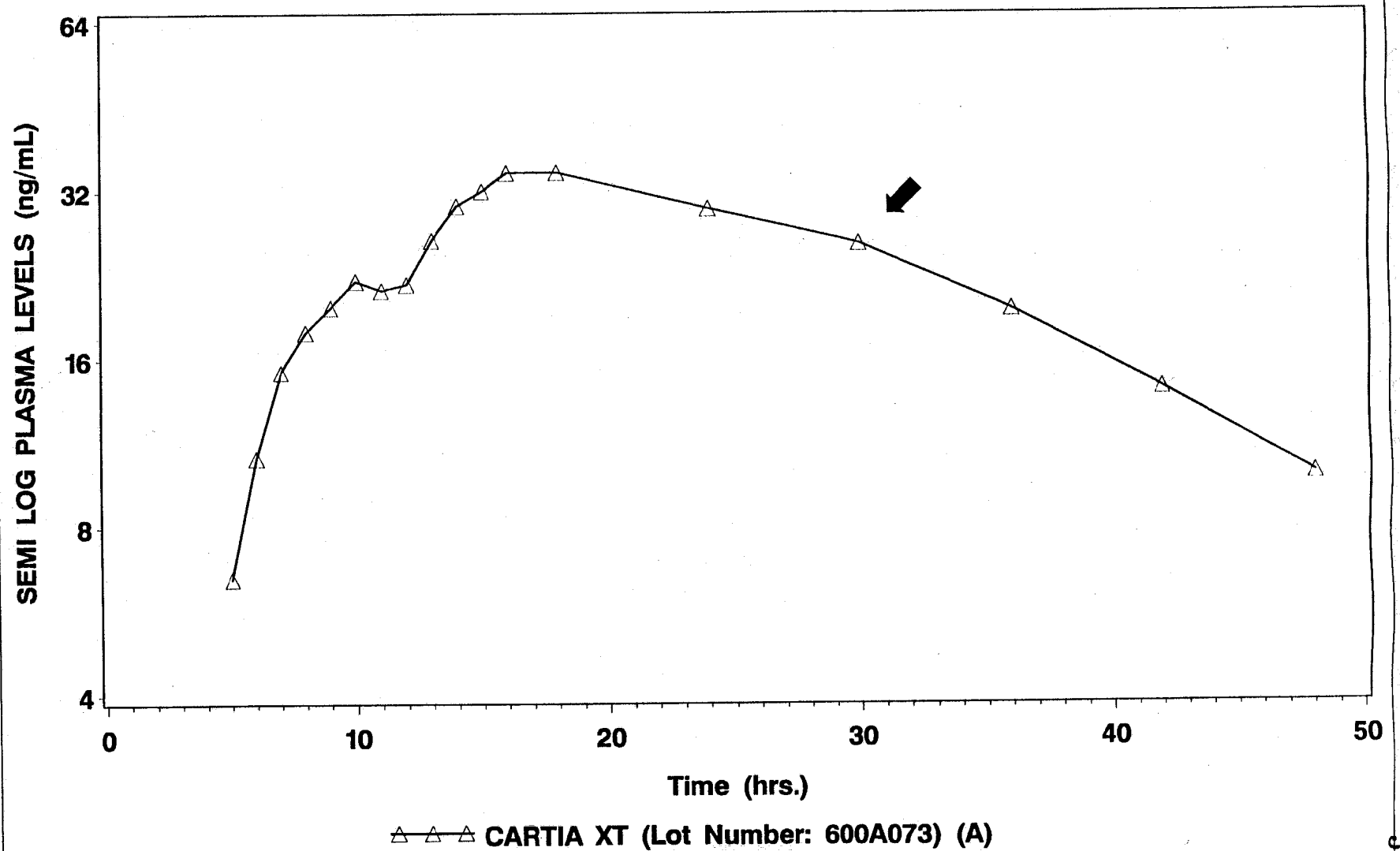
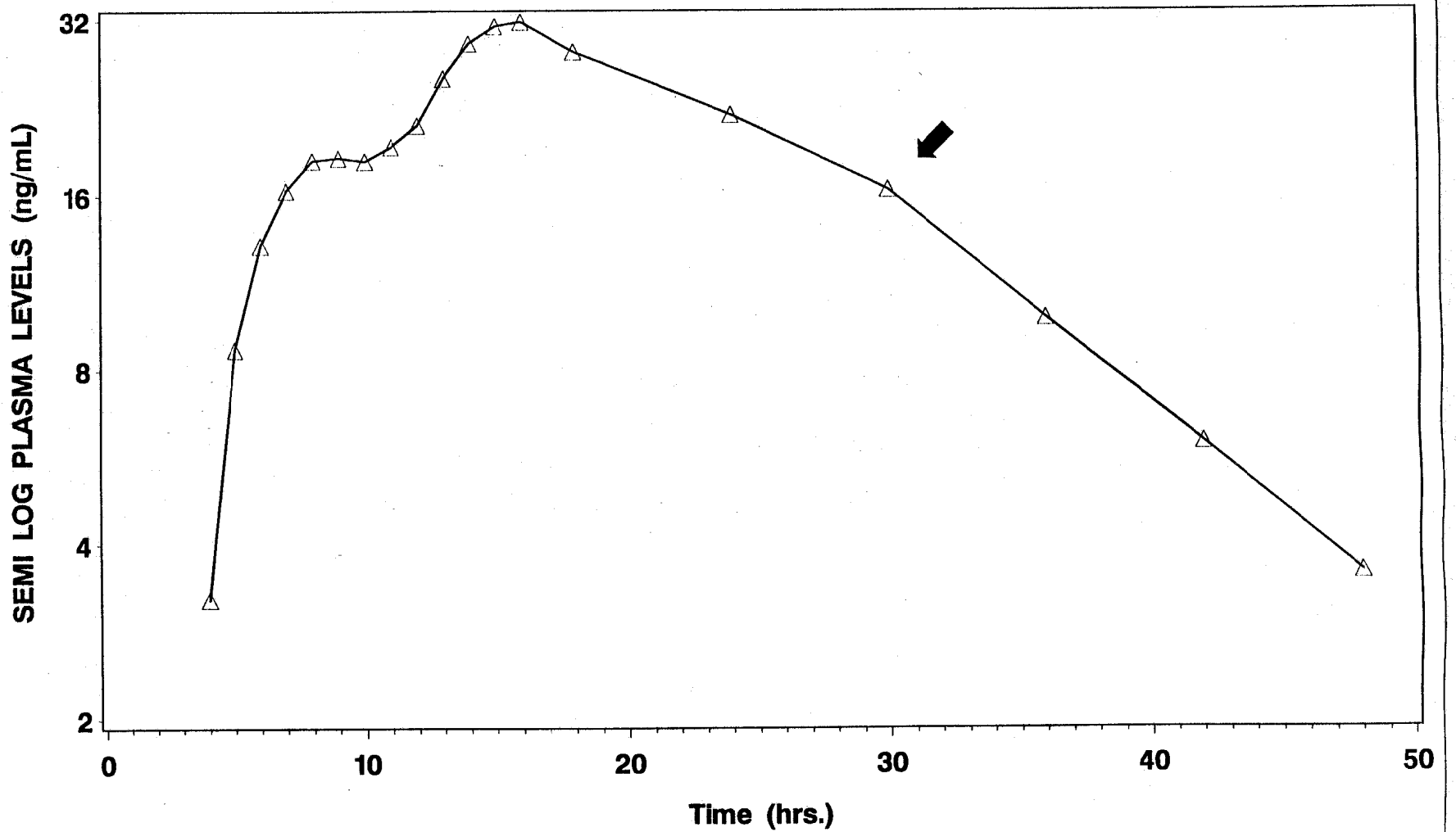


FIGURE 3.52

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 25



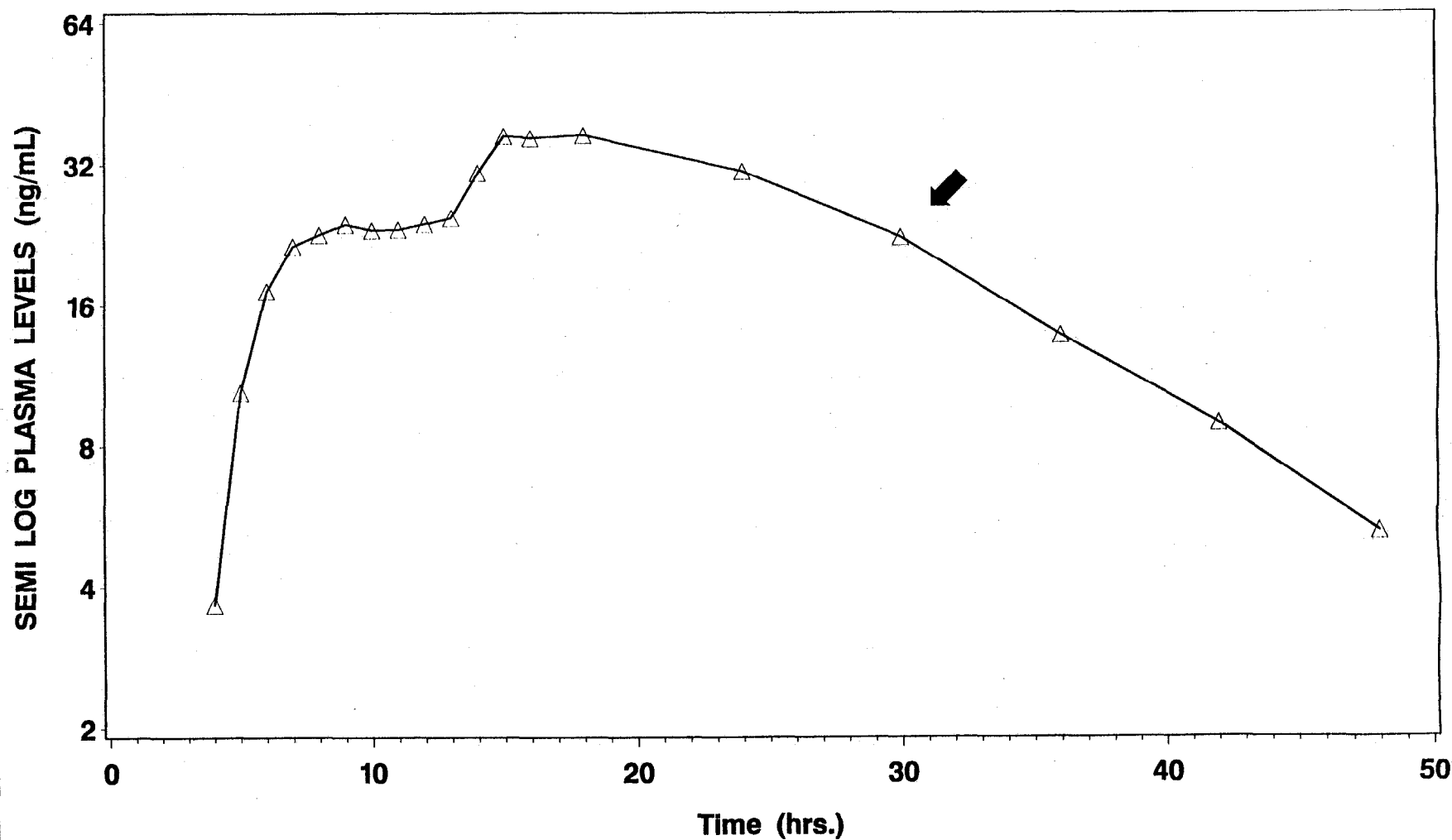
△-△-△ **CARTIA XT (Lot Number: 600A073) (A)**

FIGURE 3.53

528

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 26



△-△-△ **CARTIA XT (Lot Number: 600A073) (A)**

FIGURE 3.54

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 27

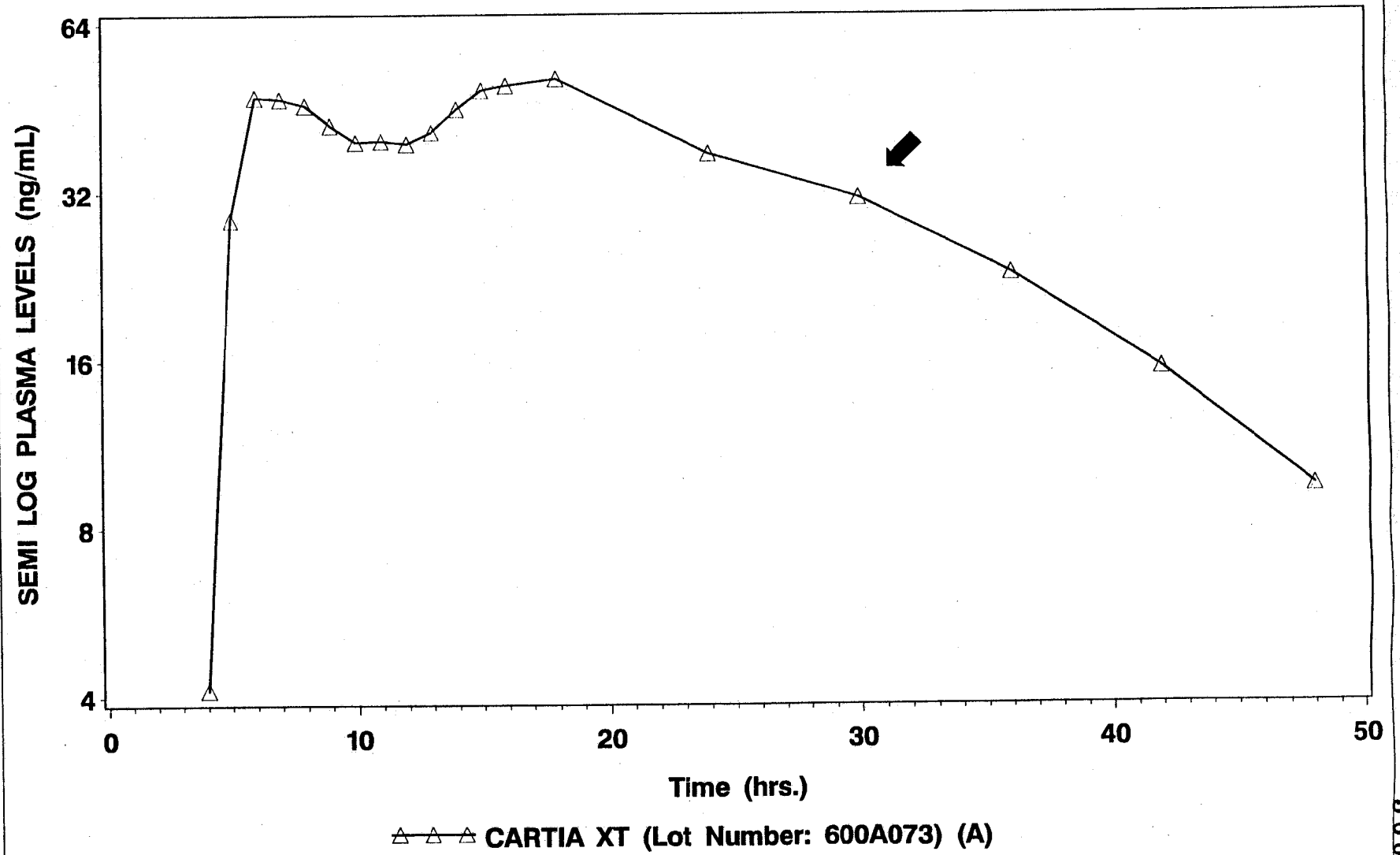
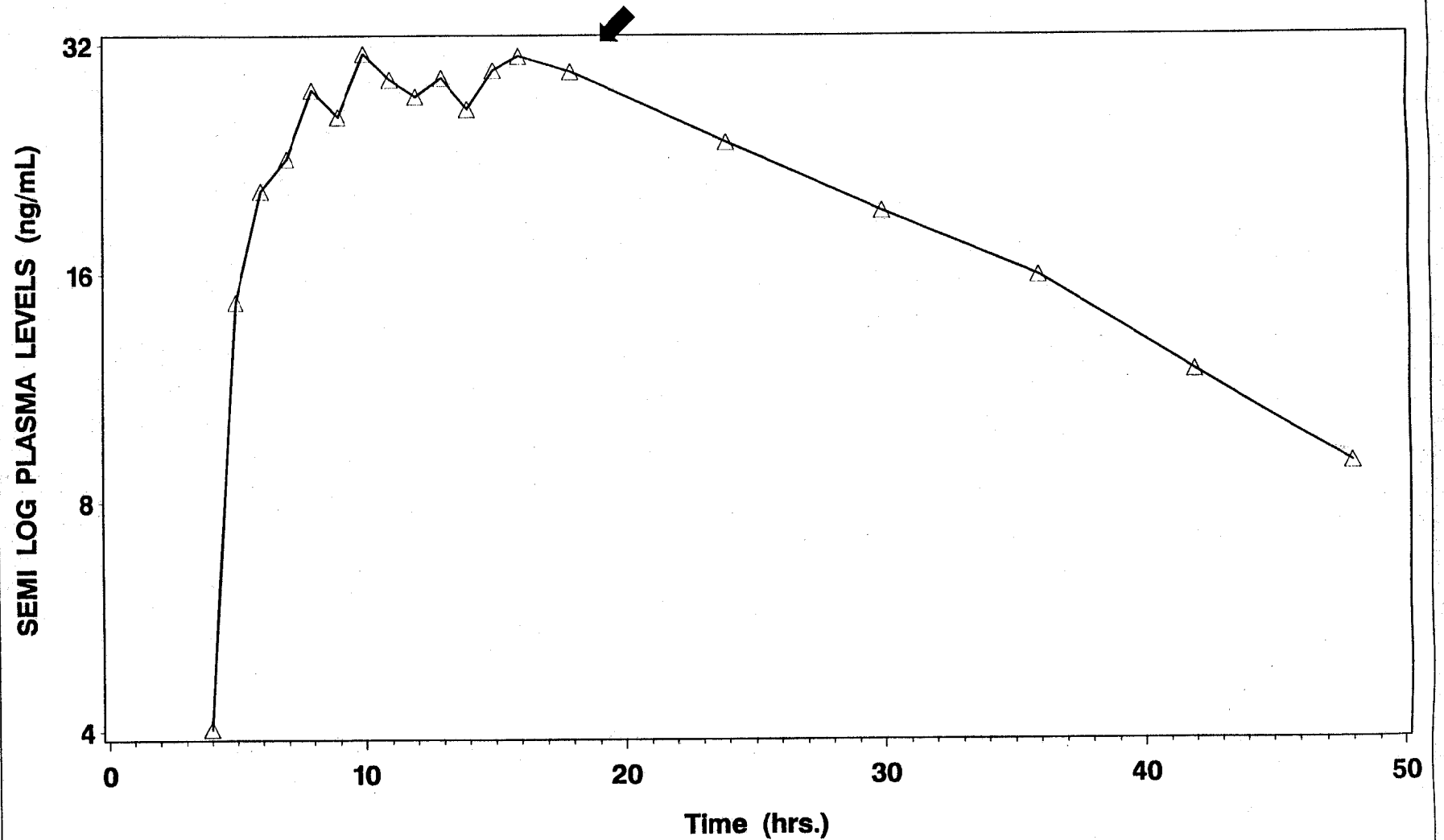


FIGURE 3.55

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 28



△-△-△ **CARTIA XT (Lot Number: 600A073) (A)**

FIGURE 3.56

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 01

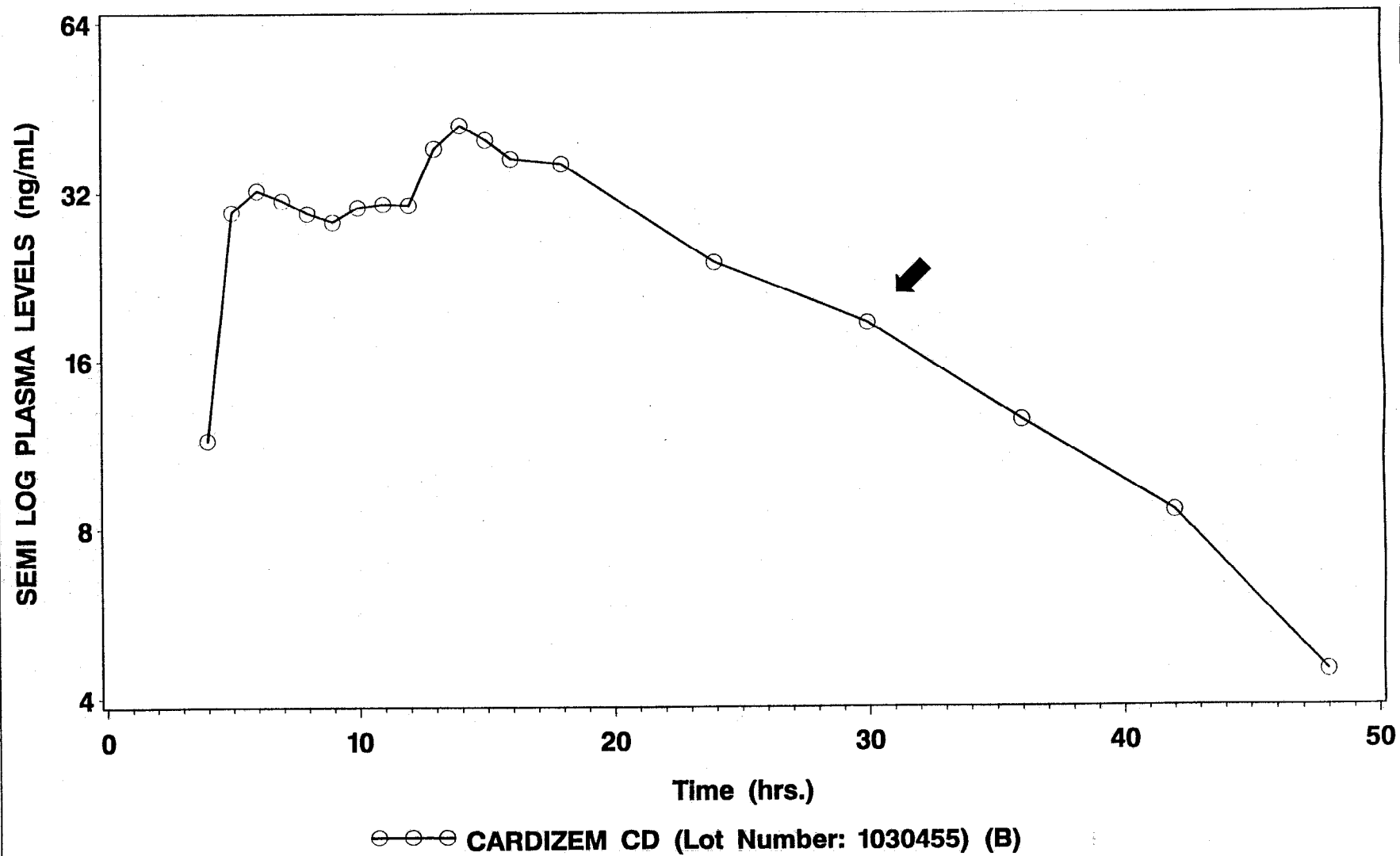
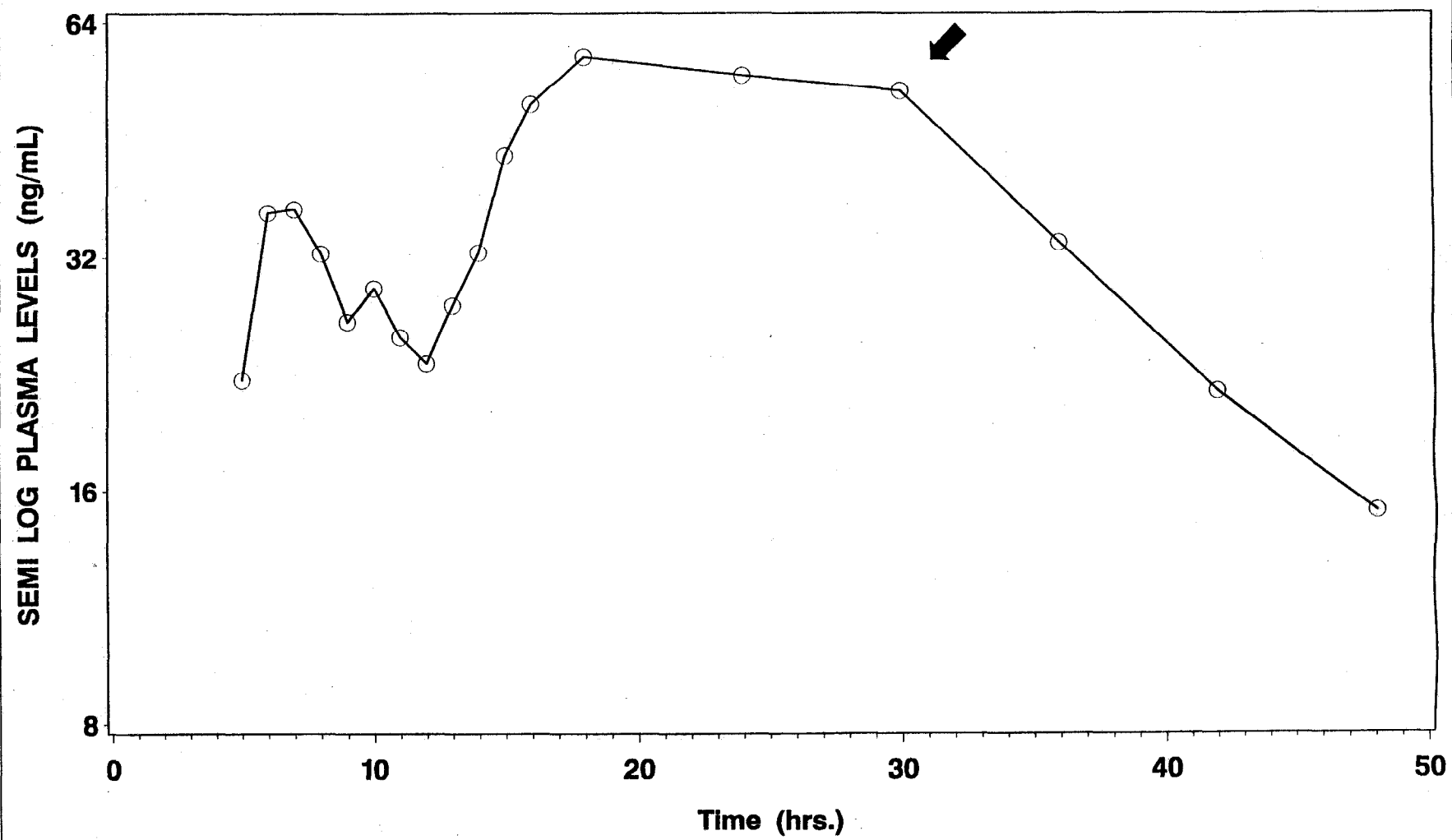


FIGURE 3.57

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 03

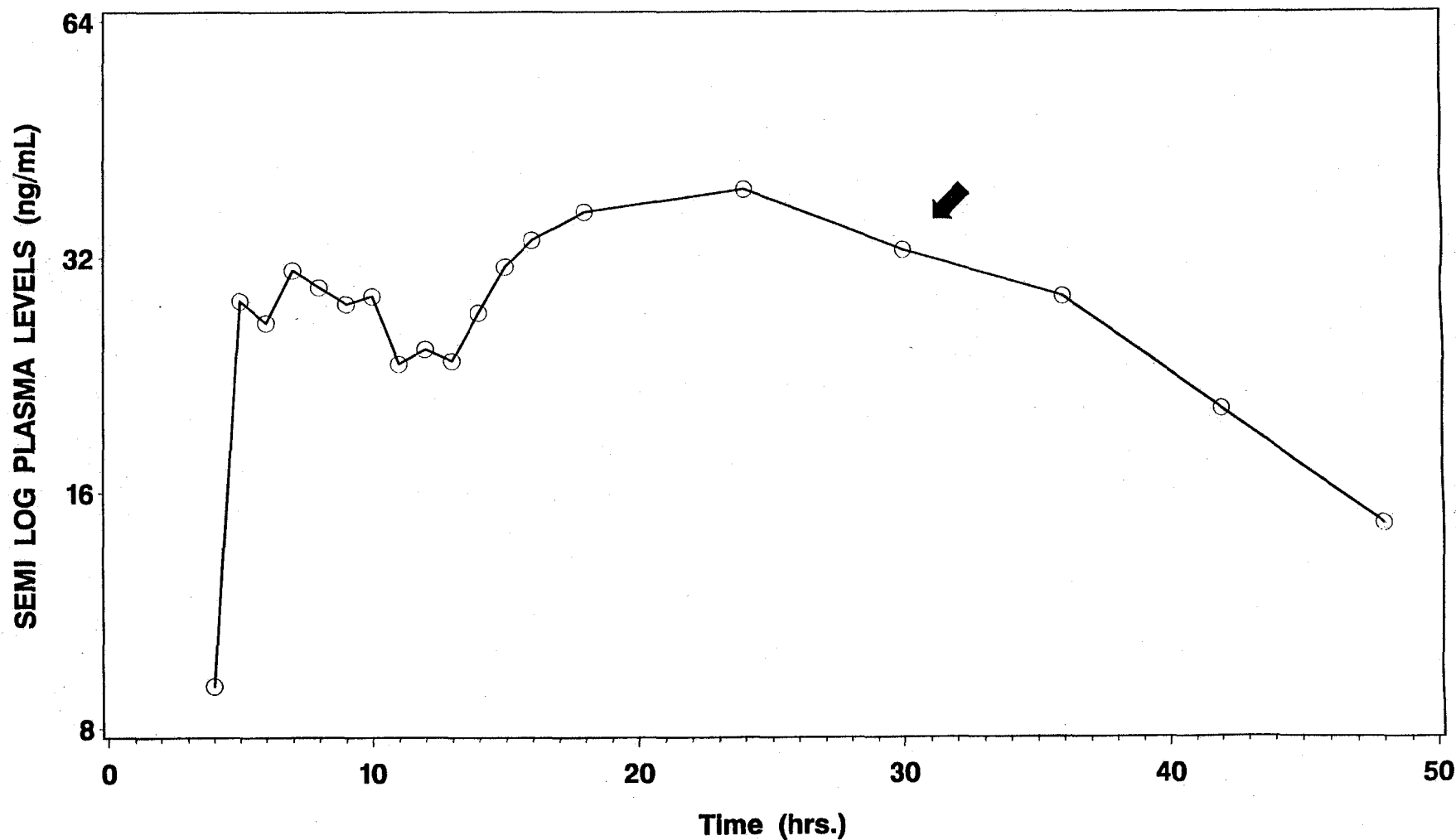


○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.58

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 04

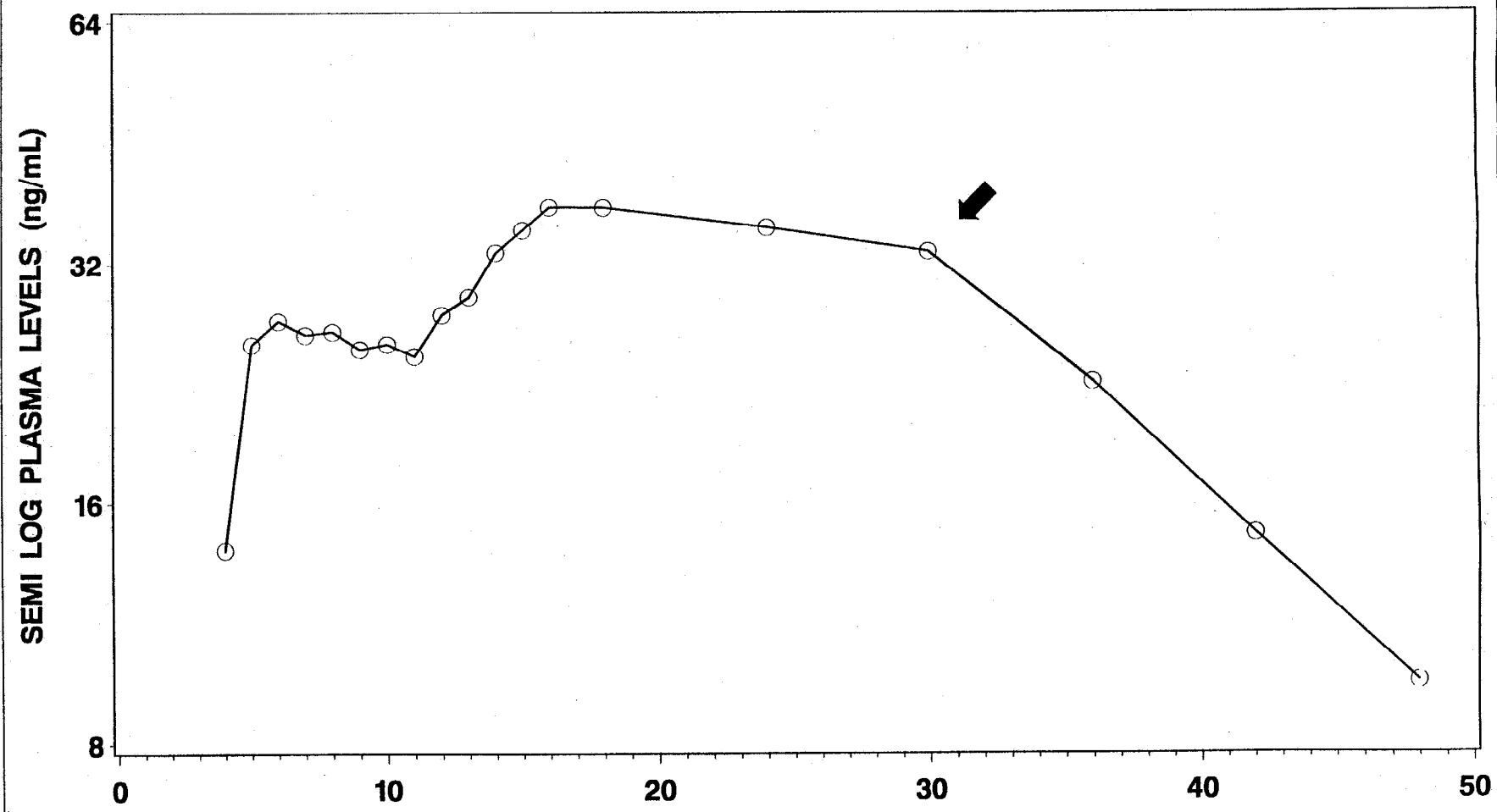


○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.59

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 05



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.60

305

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 06

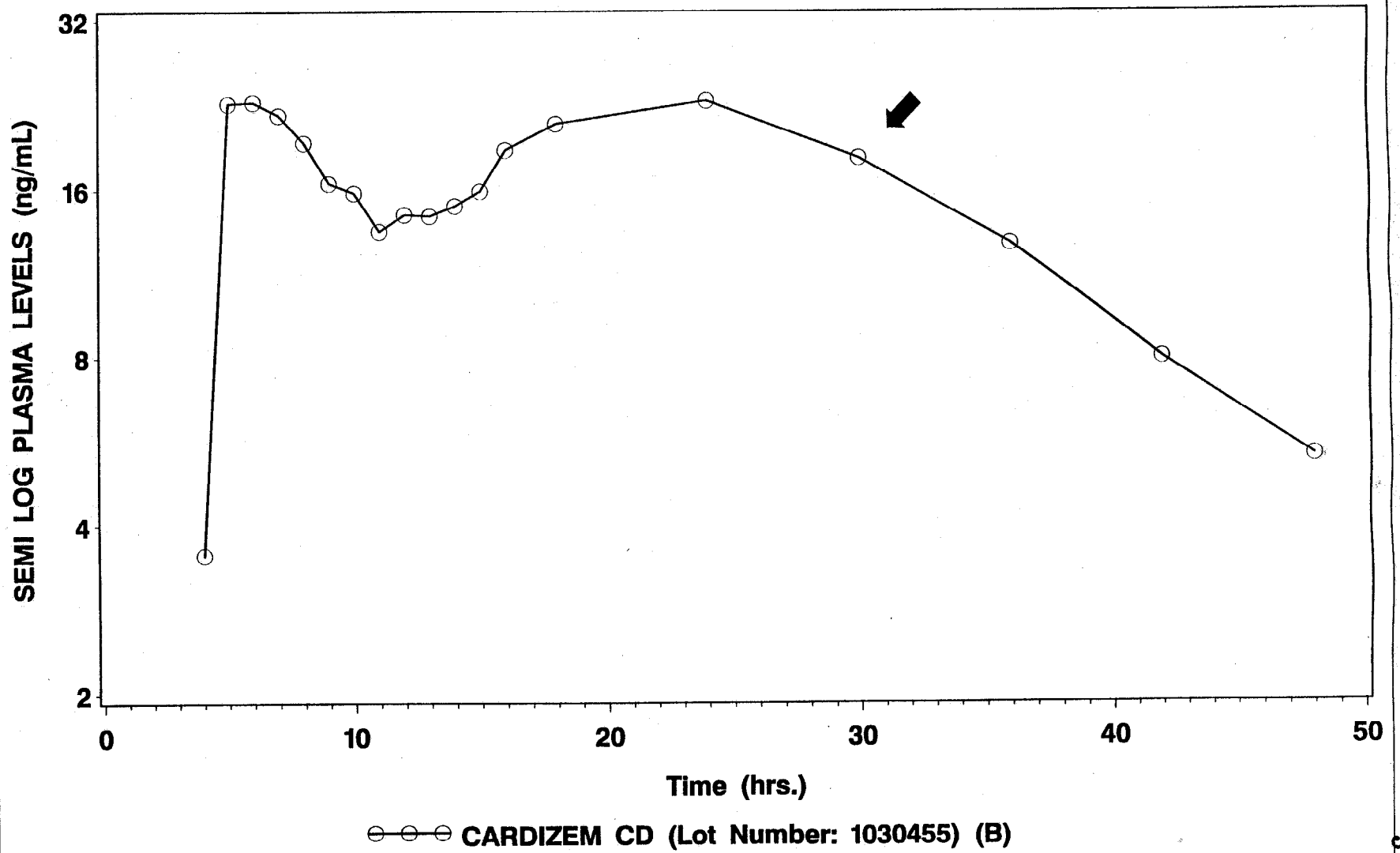
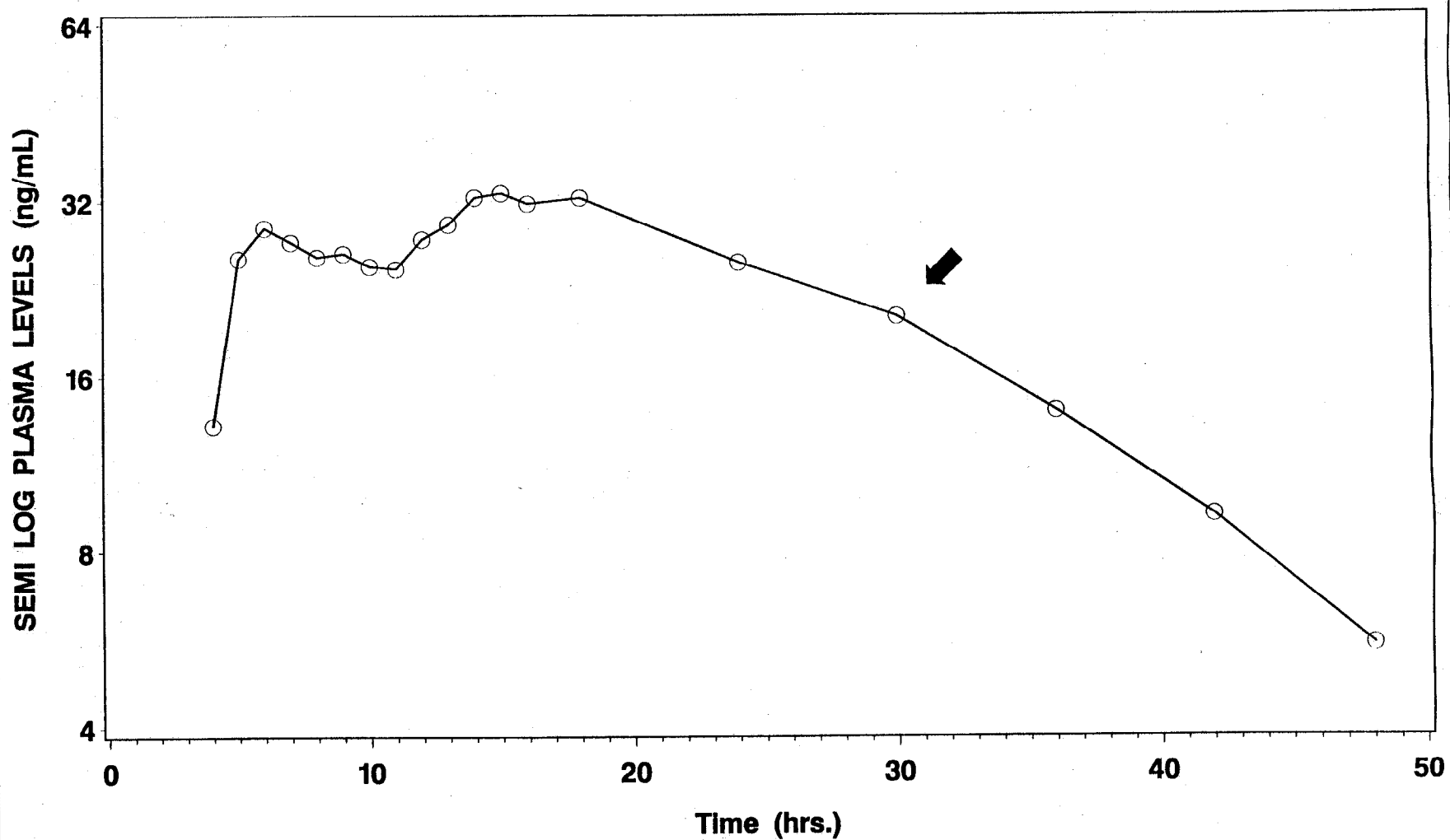


FIGURE 3.61

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 07



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.62

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 08

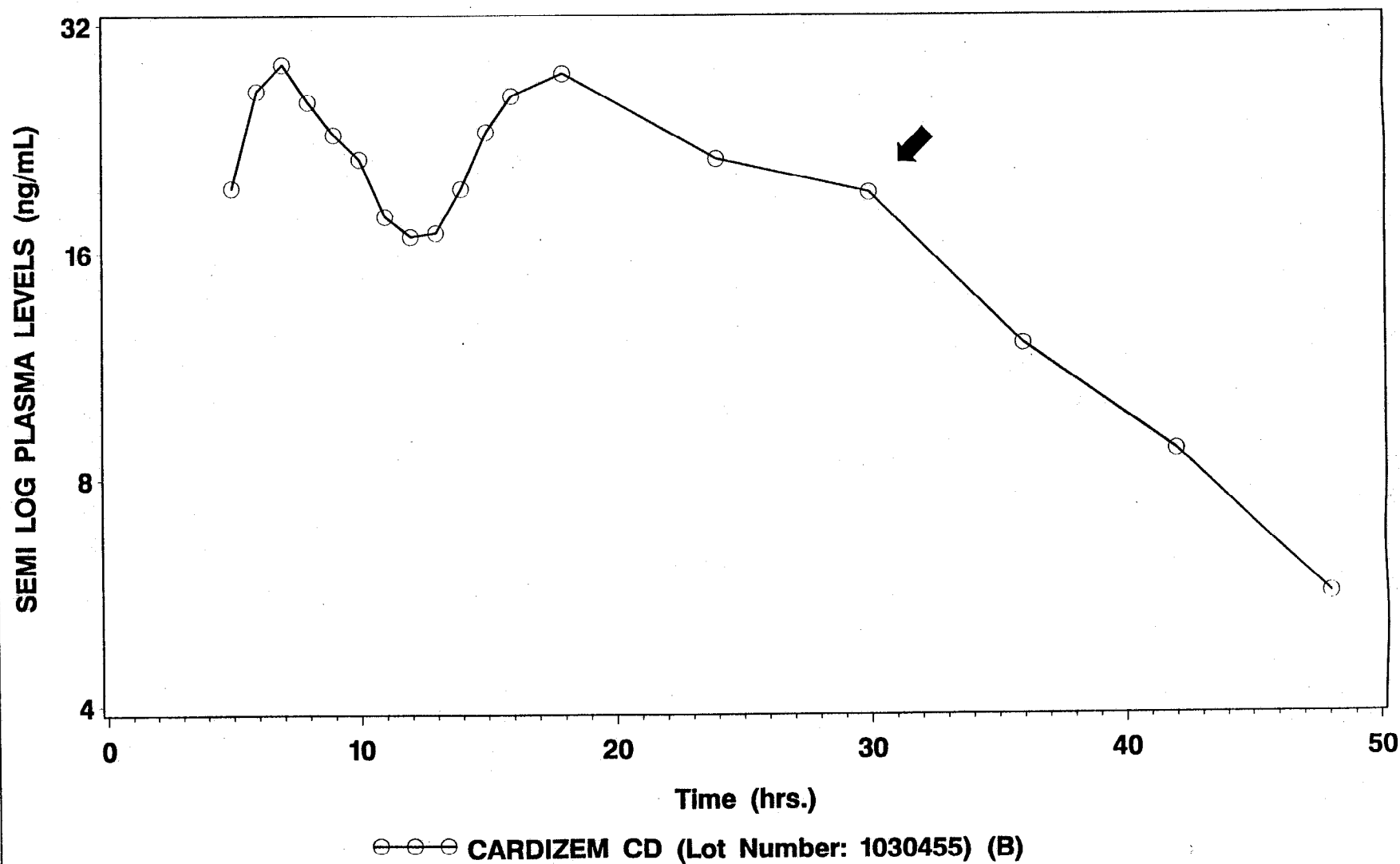
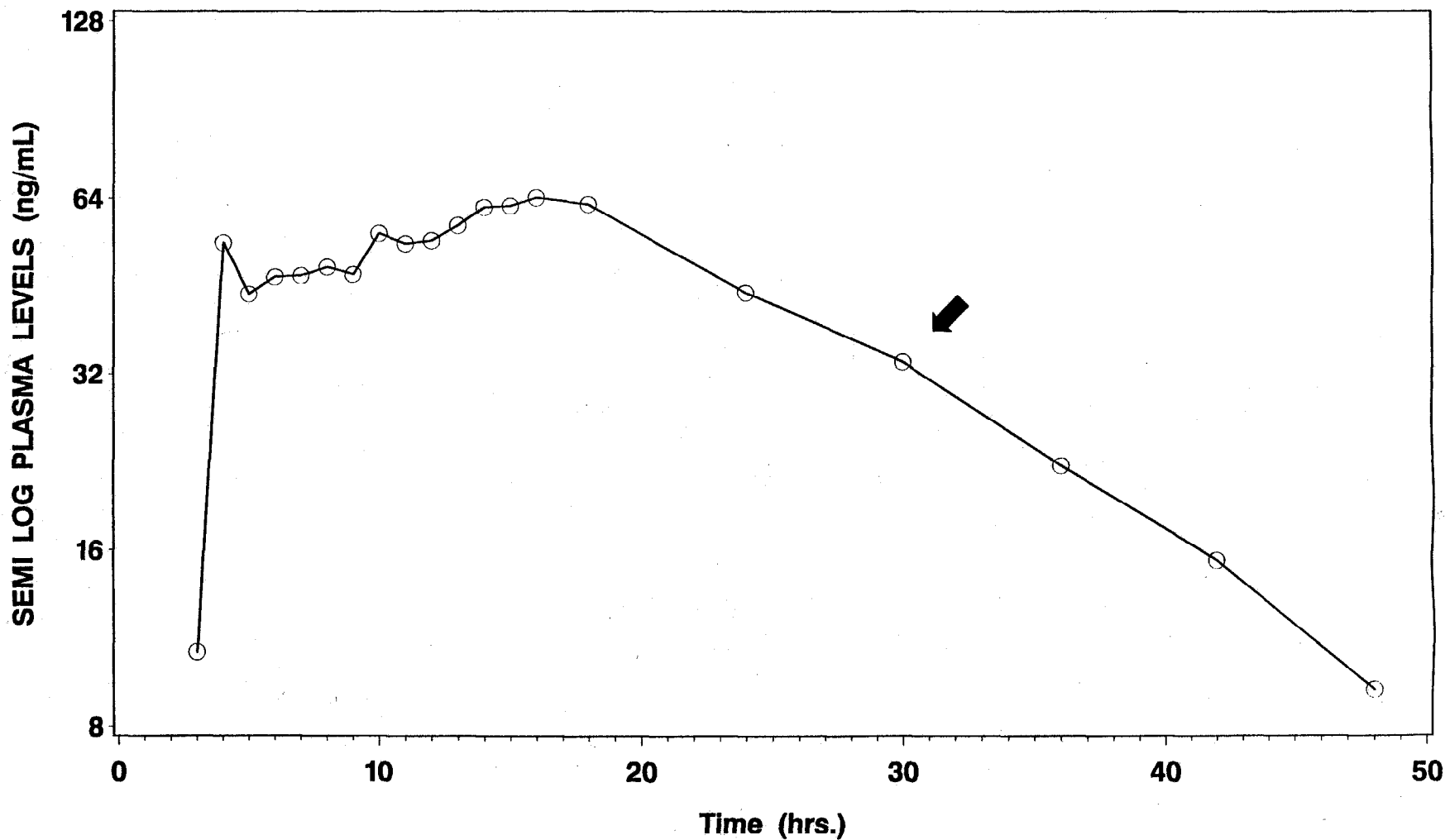


FIGURE 3.63

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

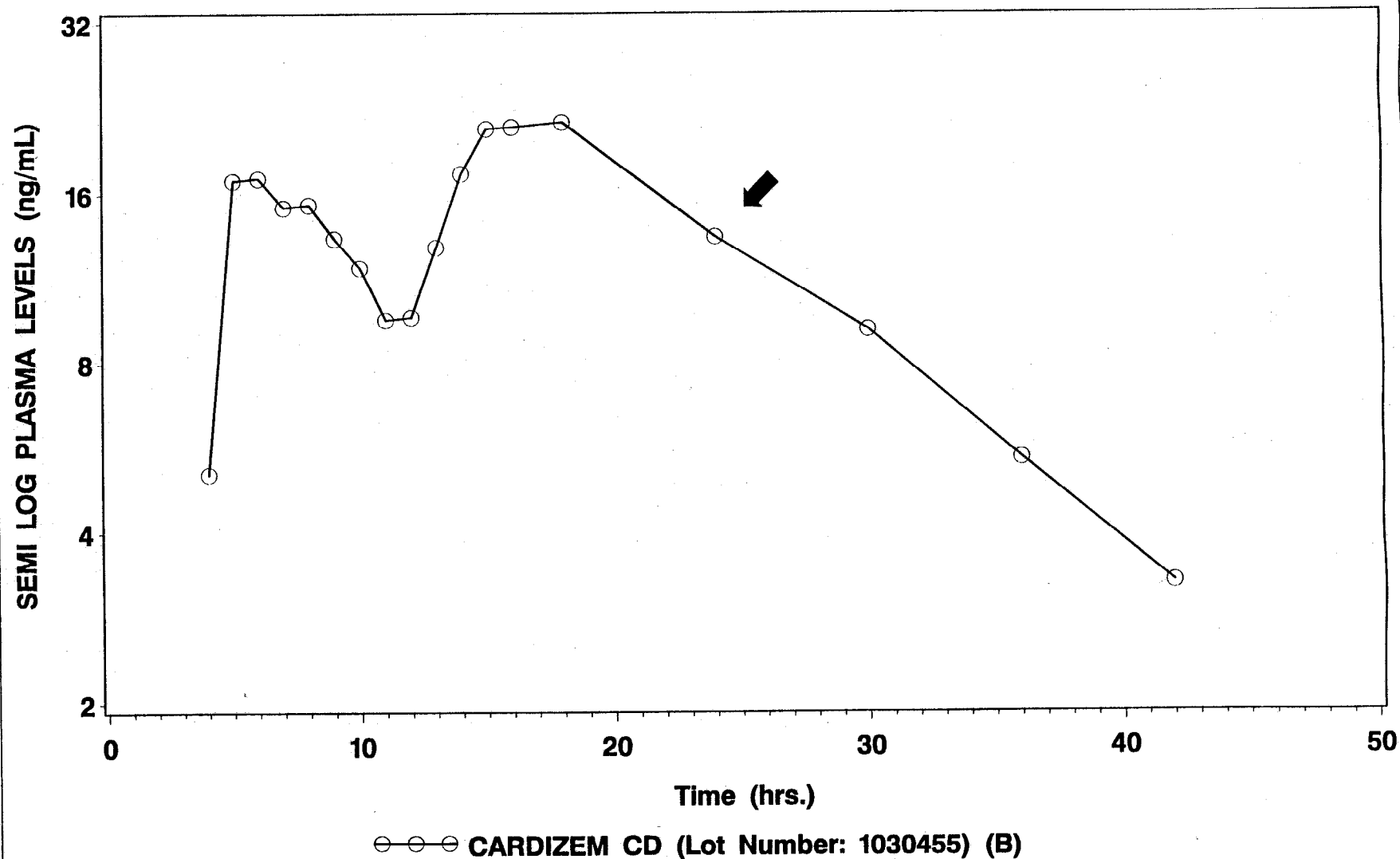
SUBJECT = 09



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.64

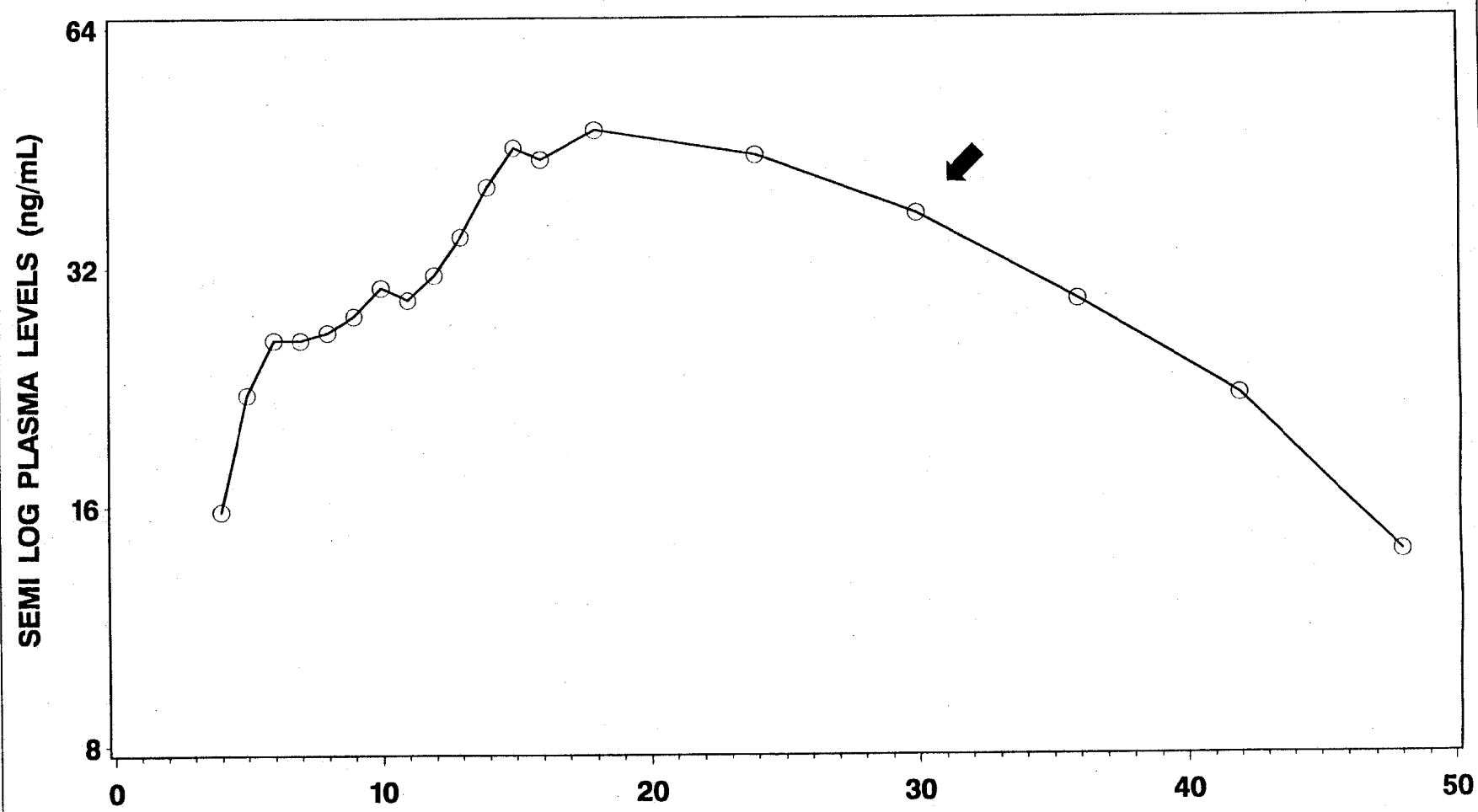
SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 10



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.65

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 11

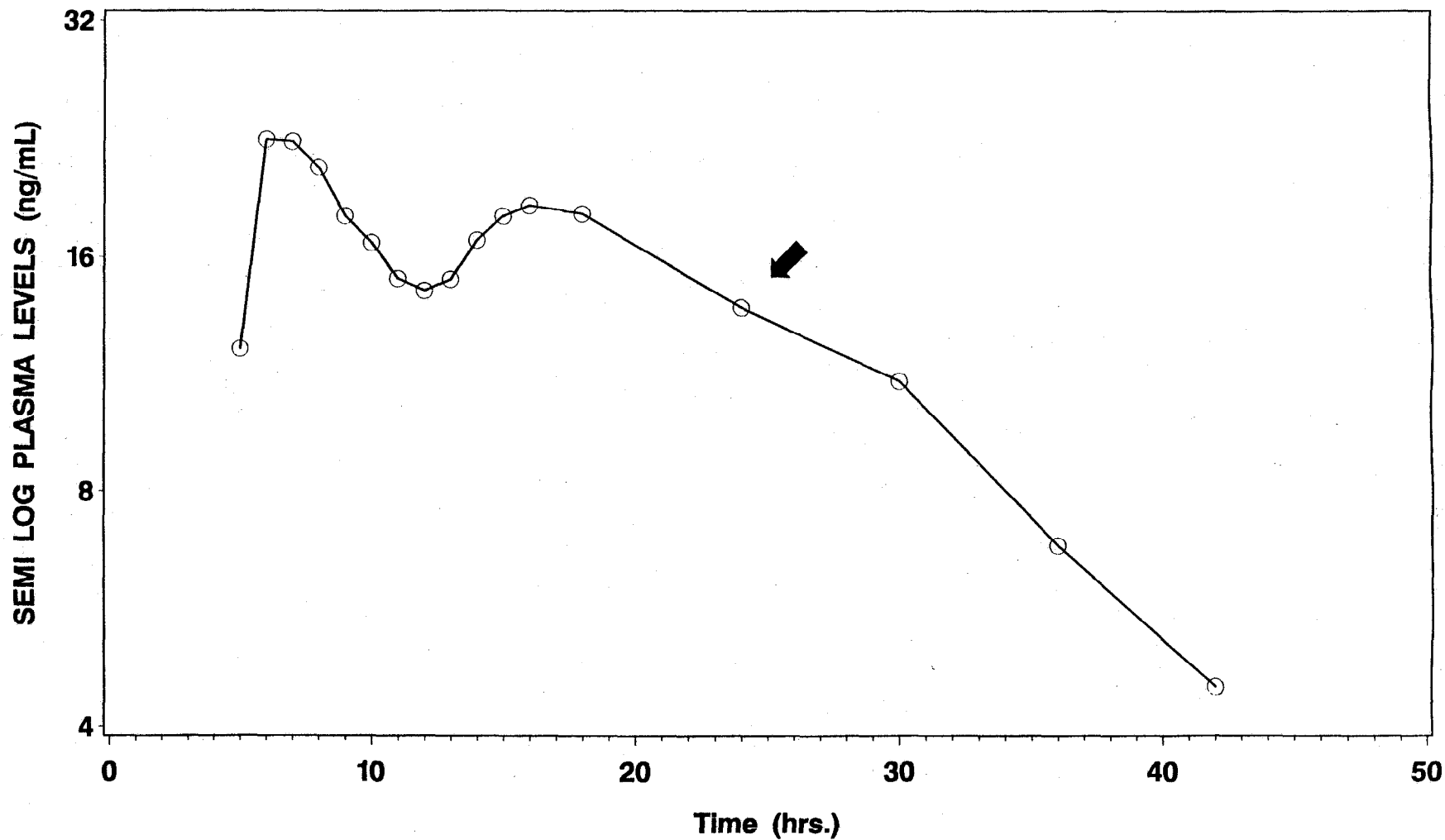


○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.66

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 12

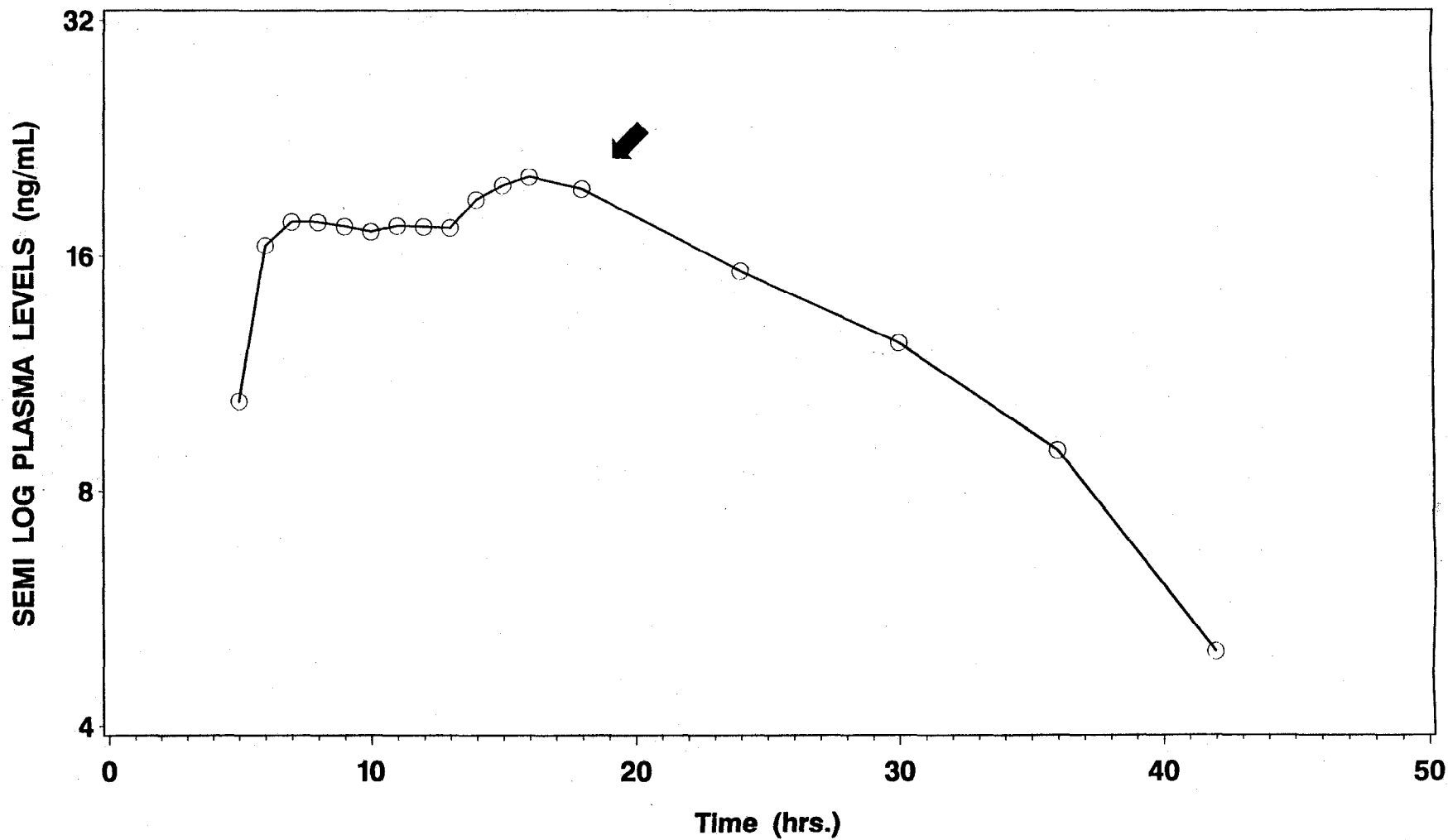


○ ○ ○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.67

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 13



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.68

373

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 14

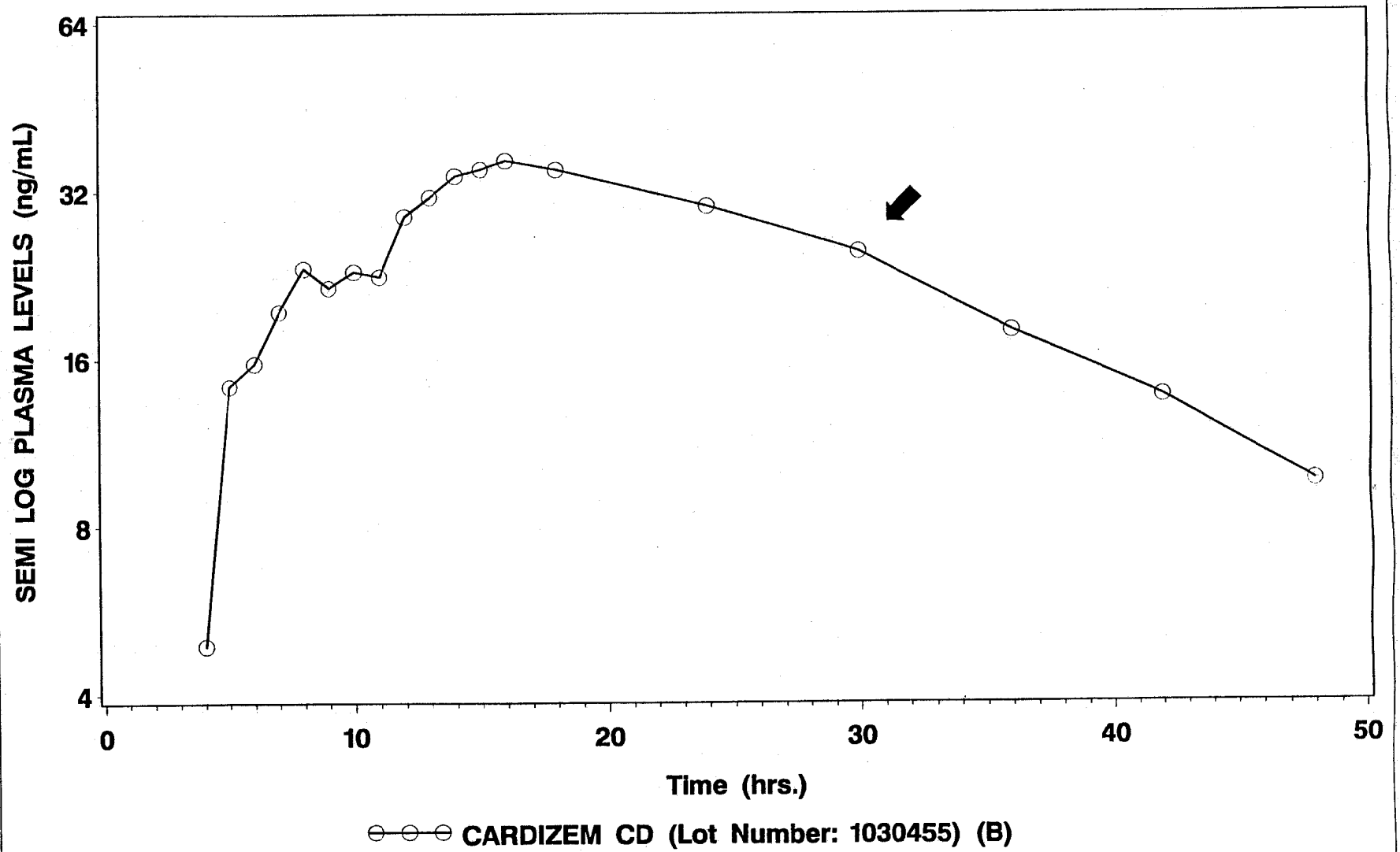


FIGURE 3.69

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 15

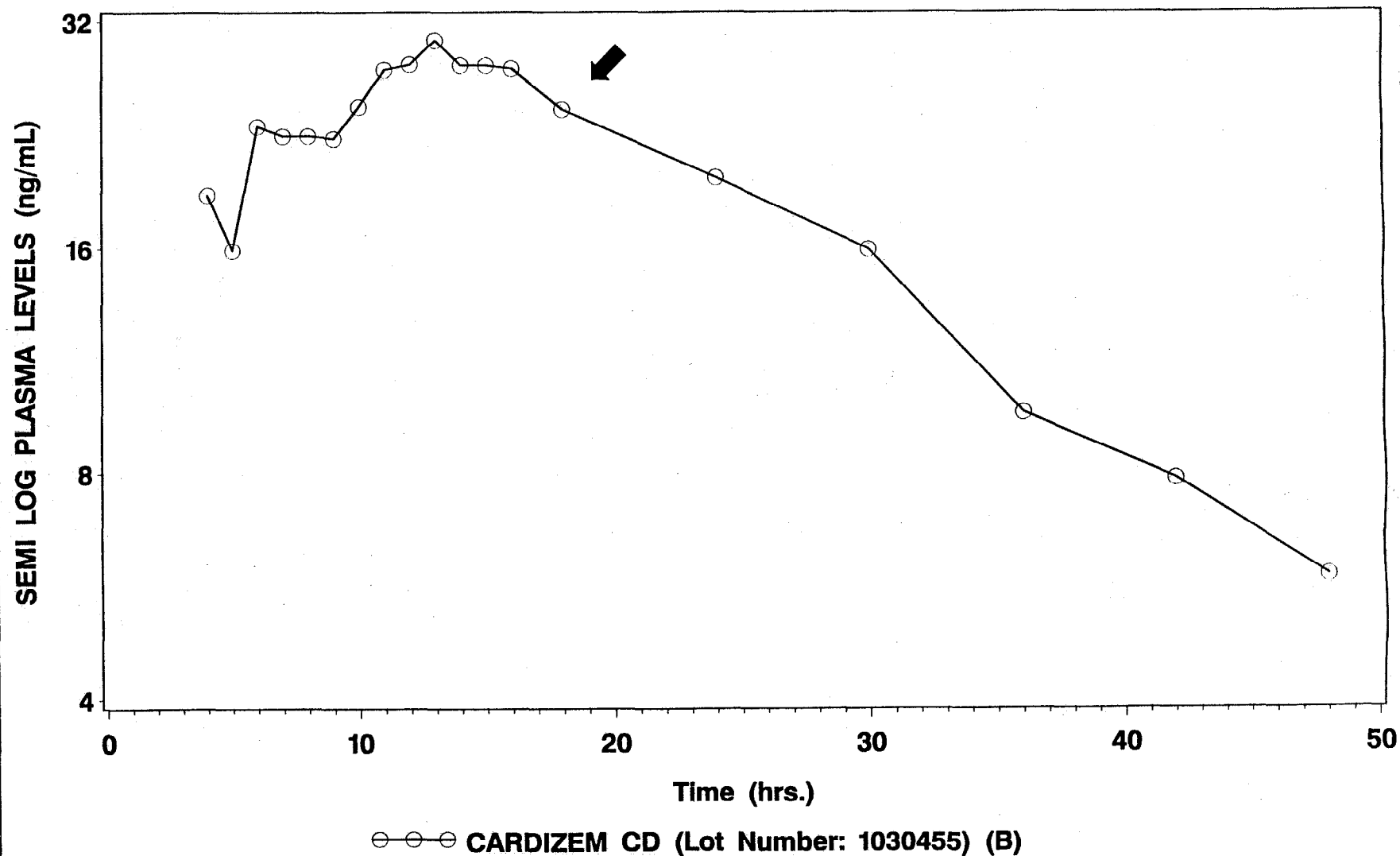


FIGURE 3.70

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 16

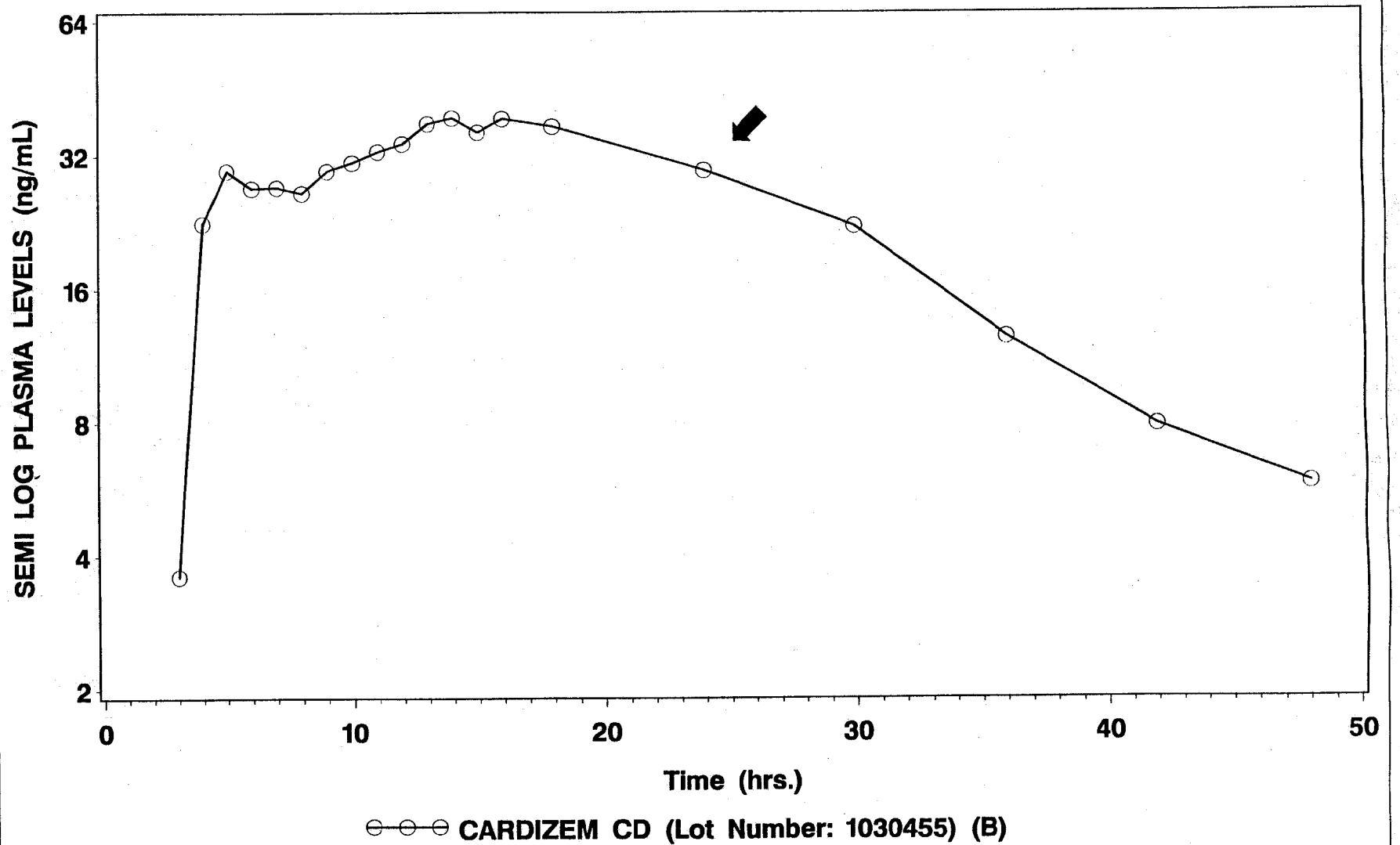


FIGURE 3.71

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 17

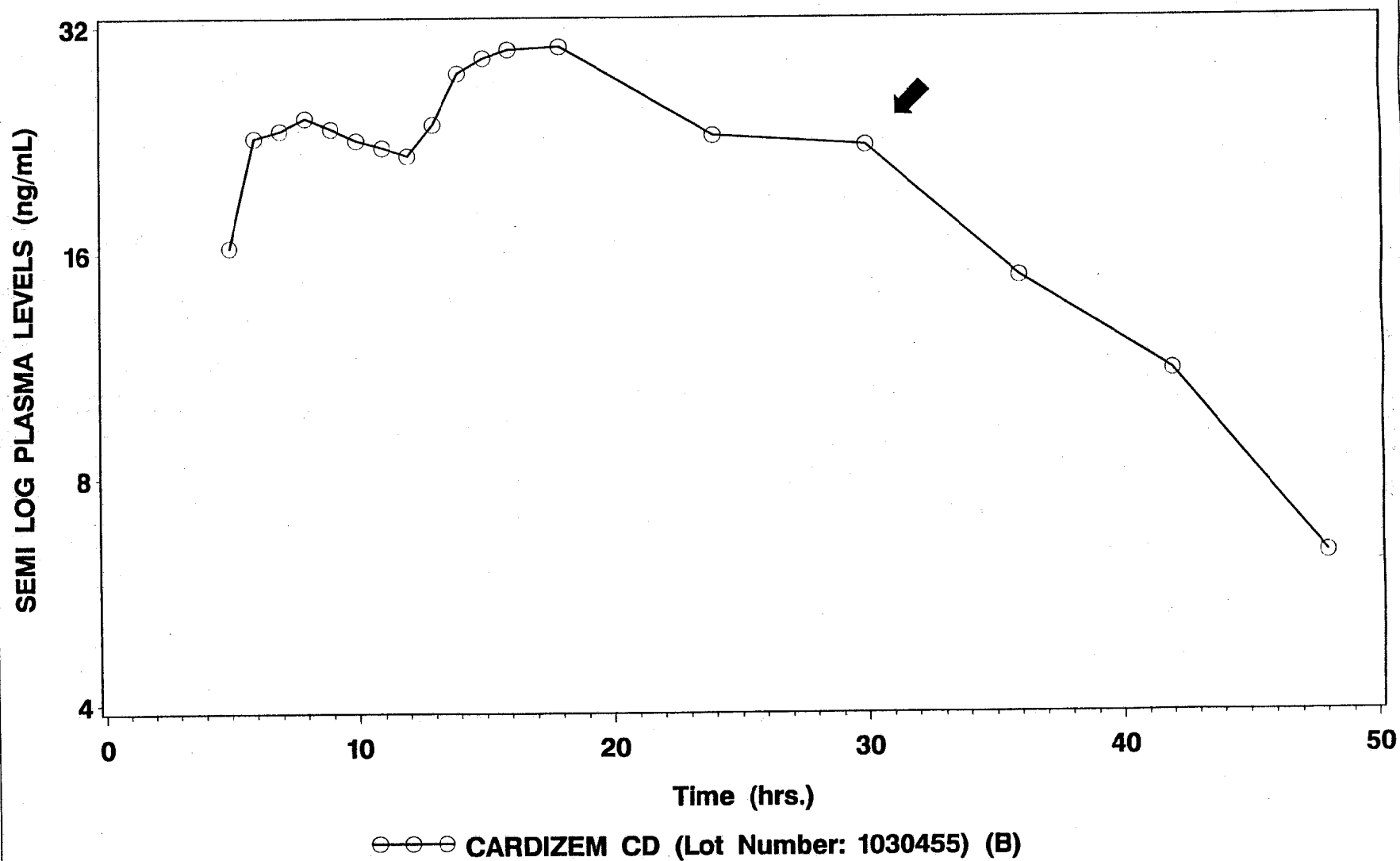


FIGURE 3.72

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 18

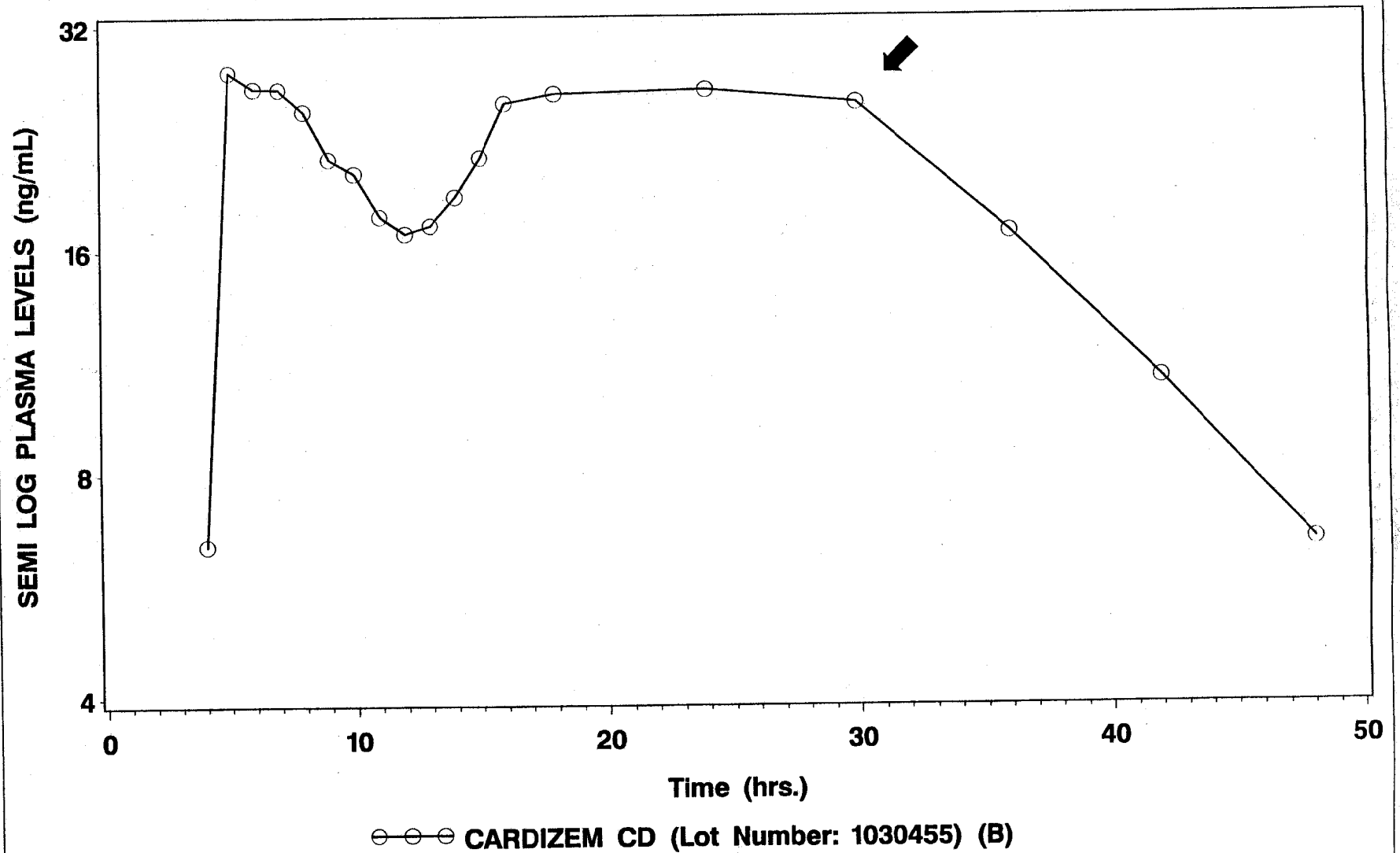
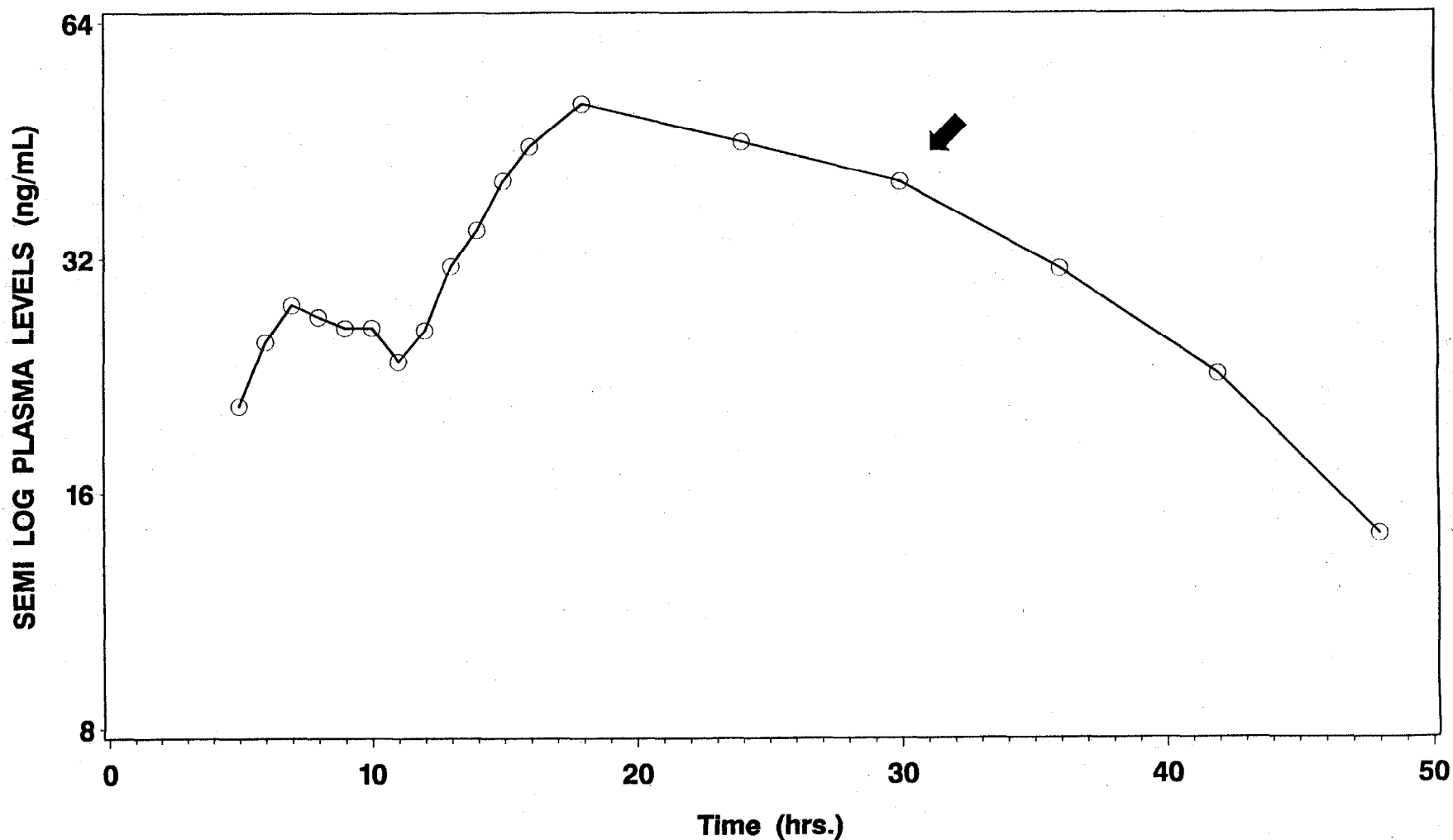


FIGURE 3.73

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

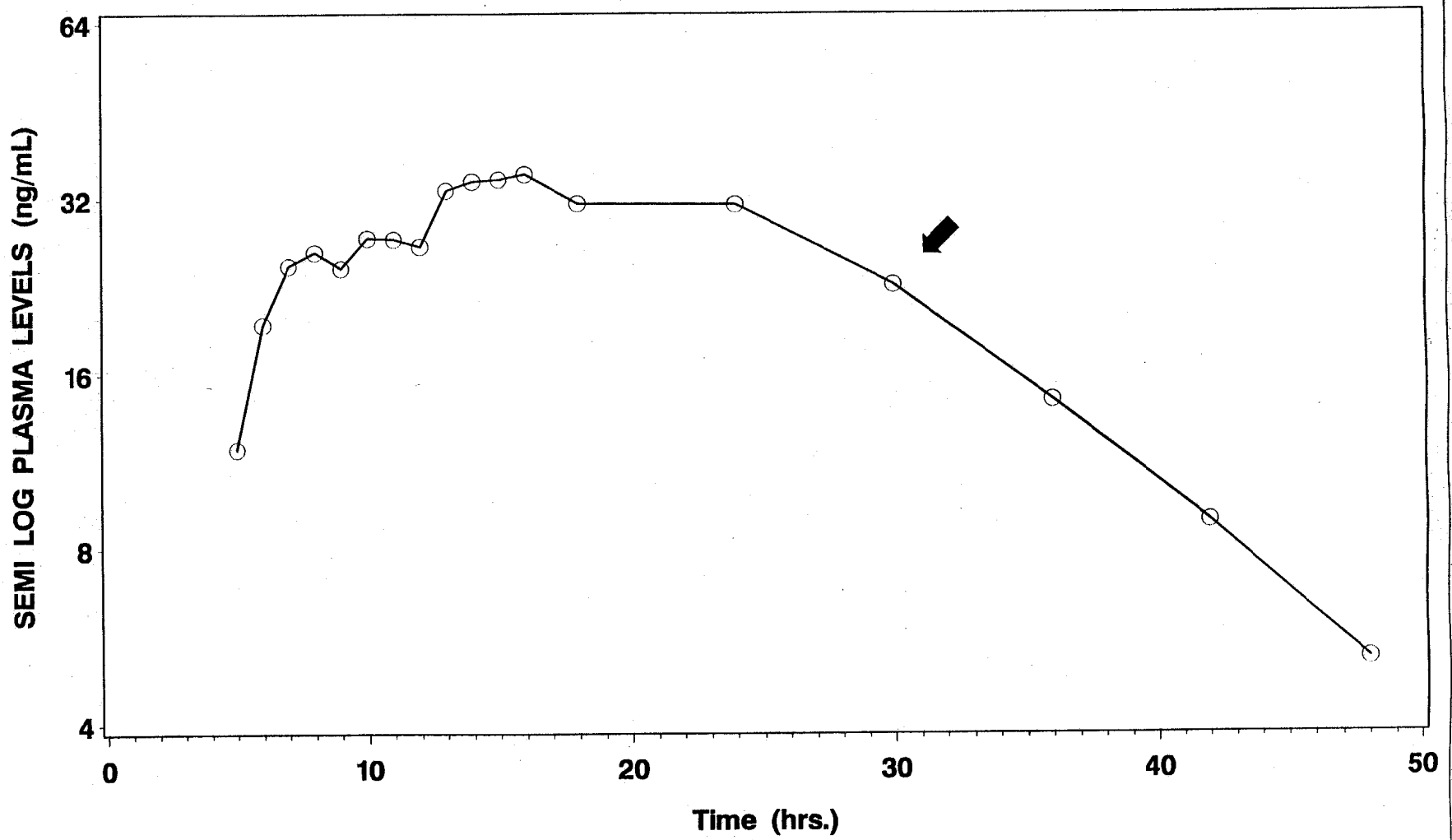
SUBJECT = 19



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.74

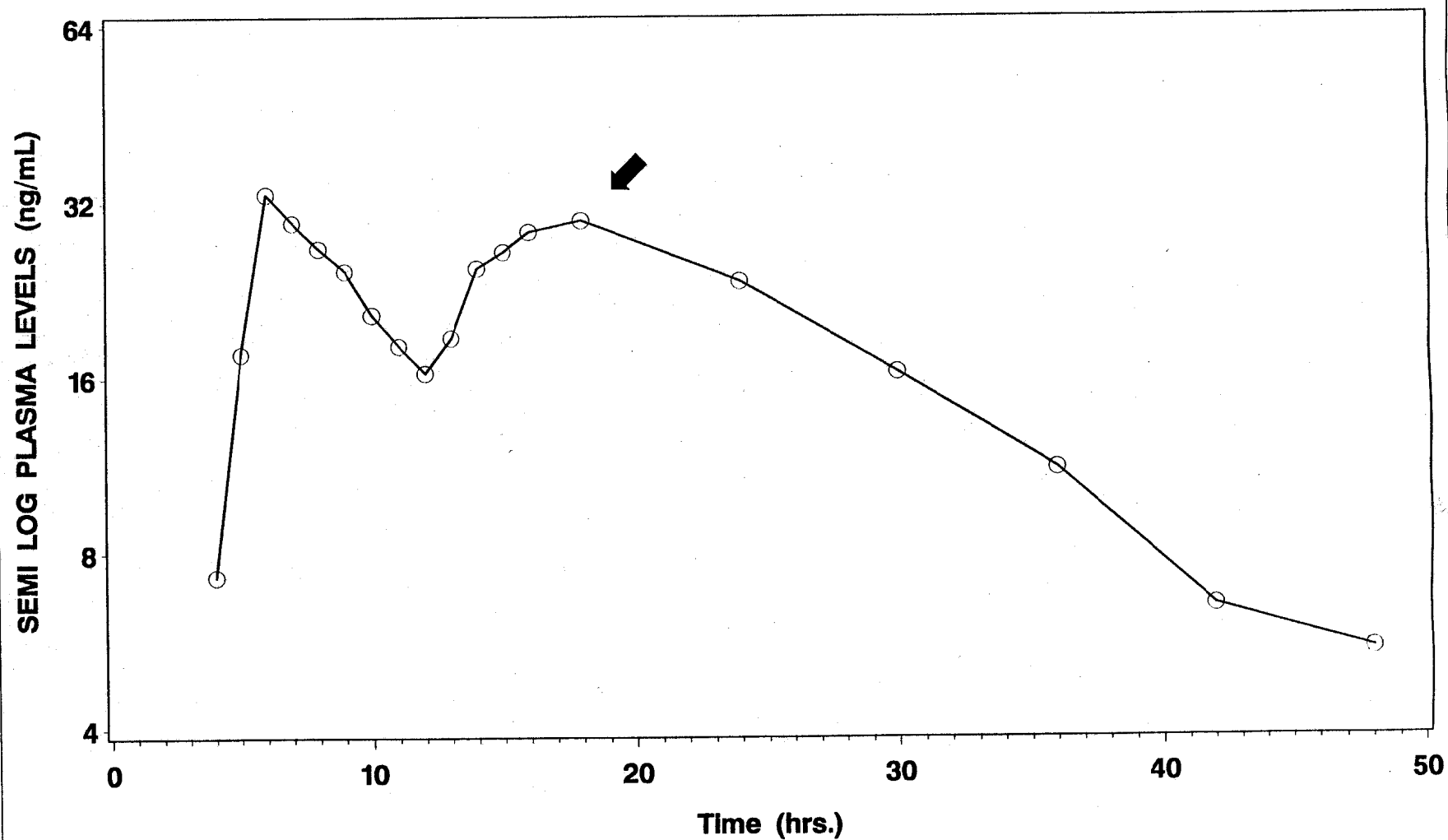
SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 20



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.75

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 21

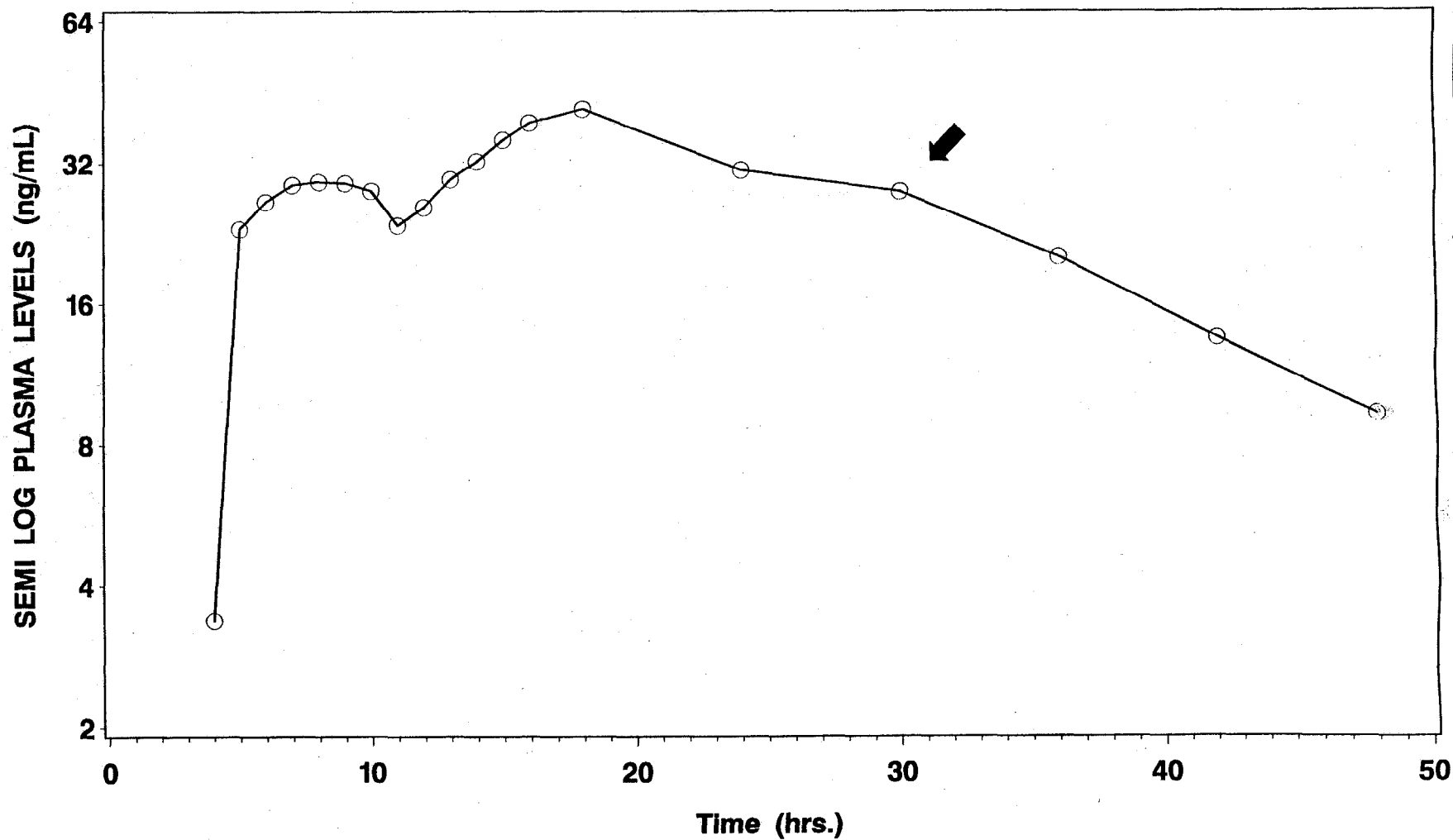


○-○-○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.76

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 22



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.77

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 23

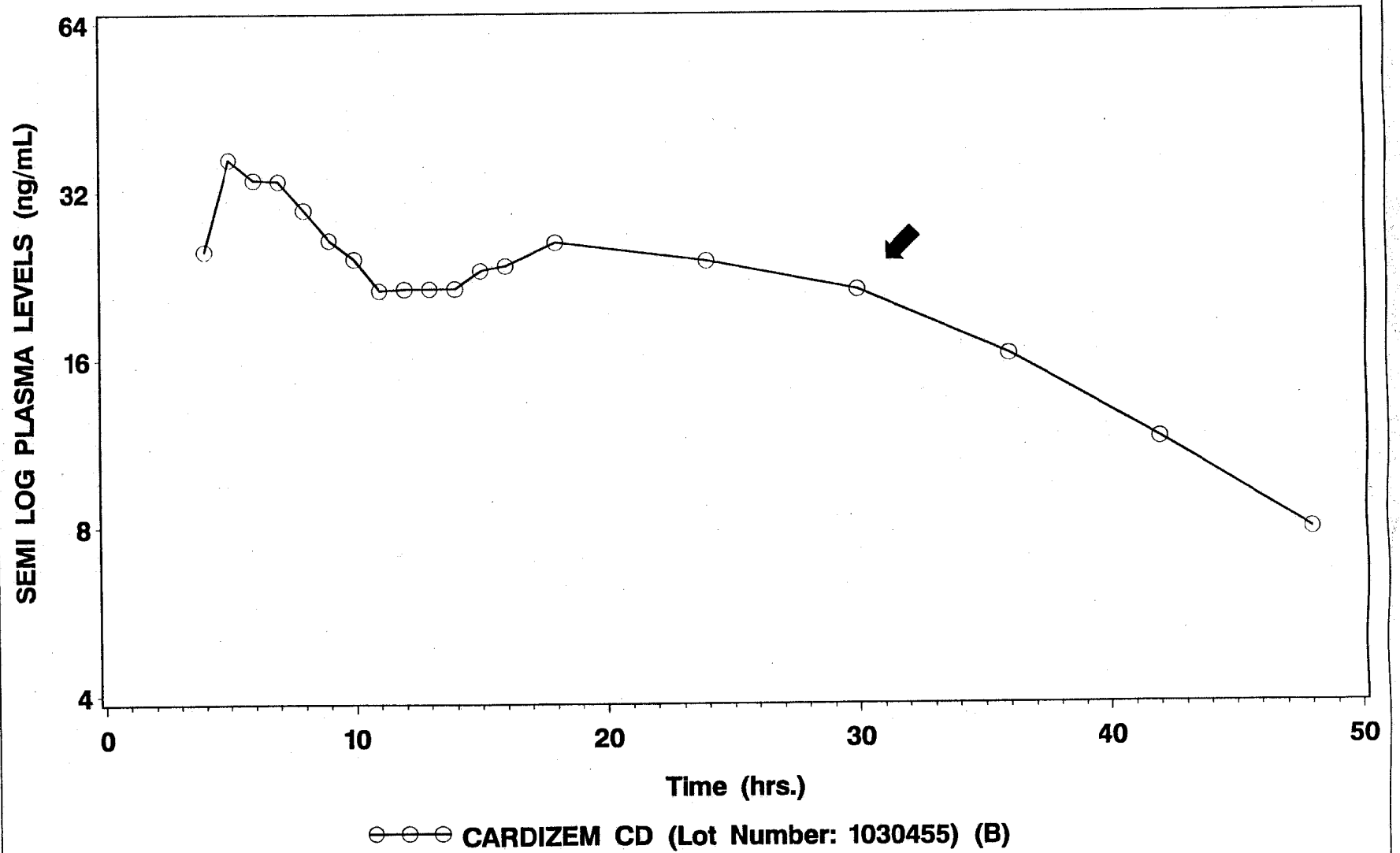


FIGURE 3.78

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 24

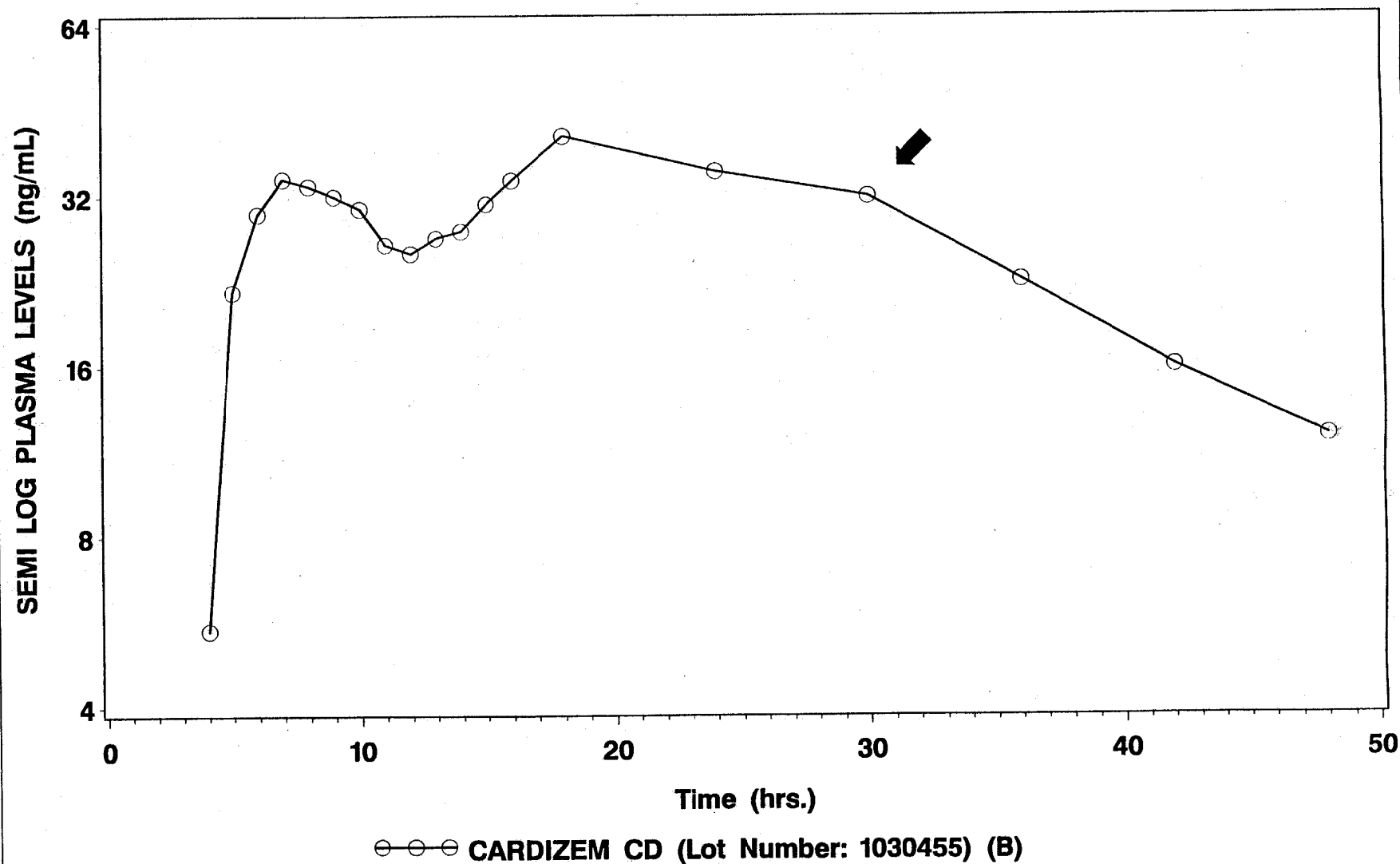
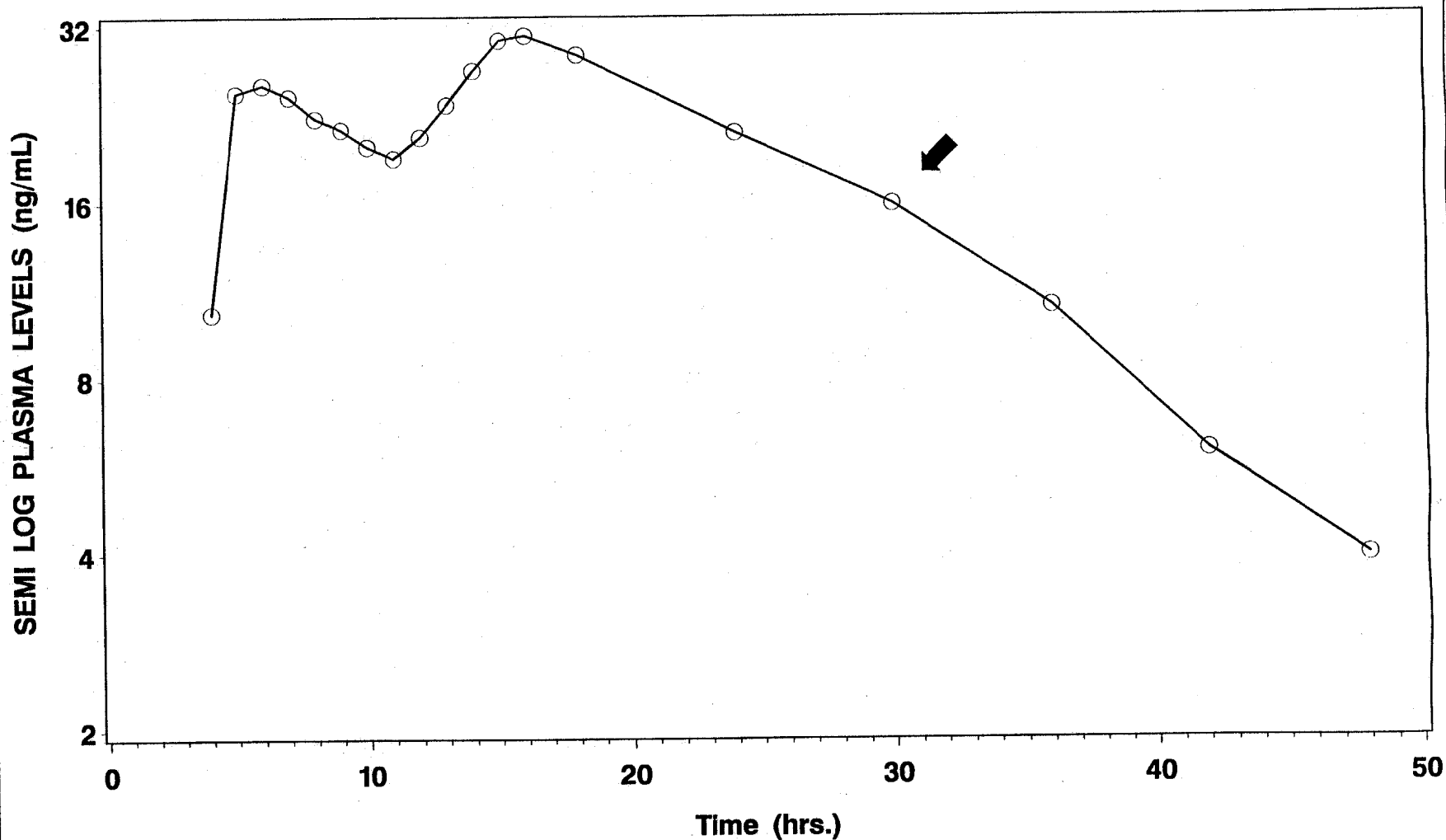


FIGURE 3.79

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 25



○ ○ ○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.80

332

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)
SUBJECT = 26

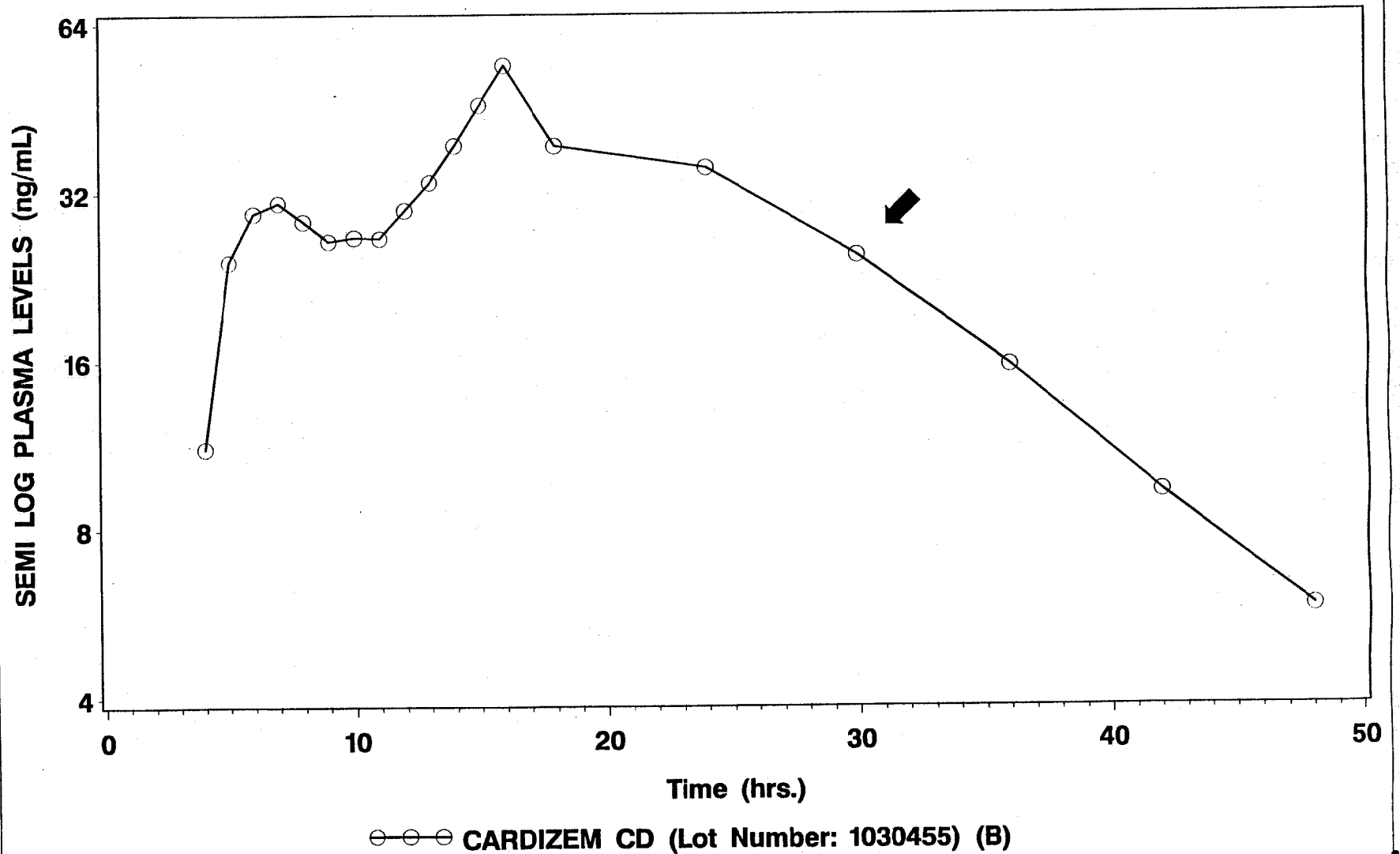
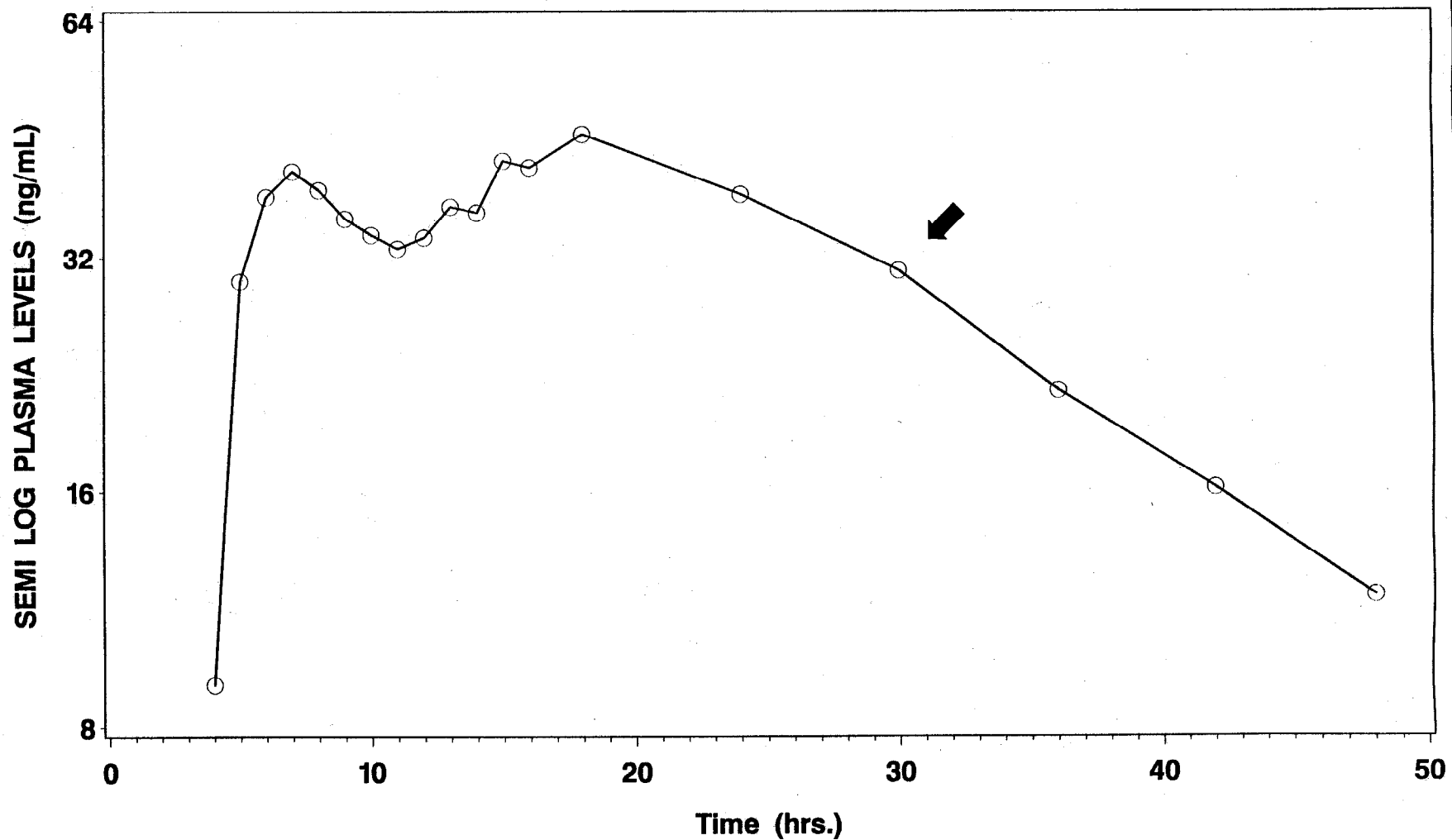


FIGURE 3.81

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 27



○—○—○ **CARDIZEM CD (Lot Number: 1030455) (B)**

FIGURE 3.82

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS (STUDY # 2443)

SUBJECT = 28

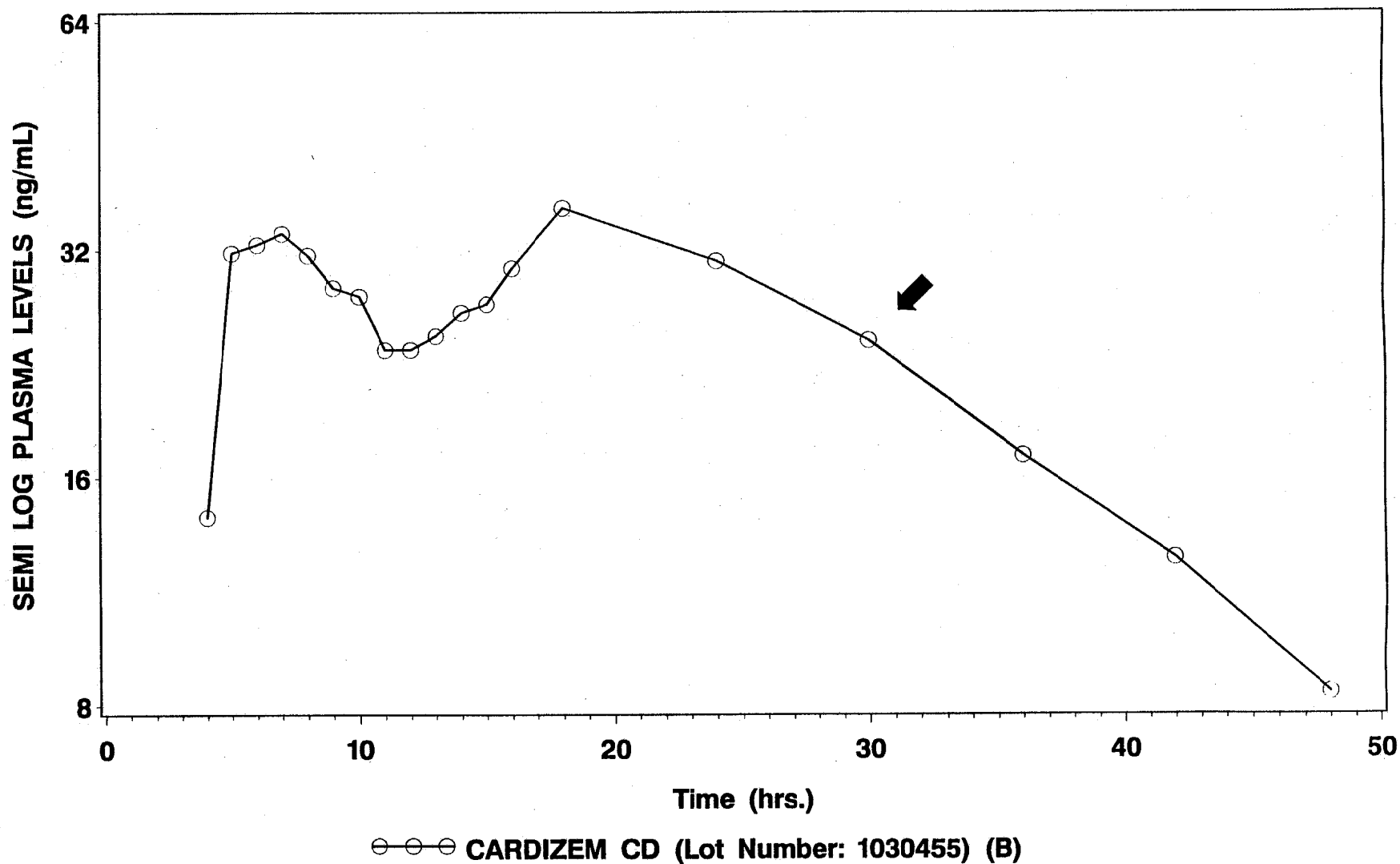


FIGURE 3.83

**Distribution of Difference of AUC (0-t) Between Formulations for N-DESMETHYLDILTIAZEM
(STUDY # 2443)**

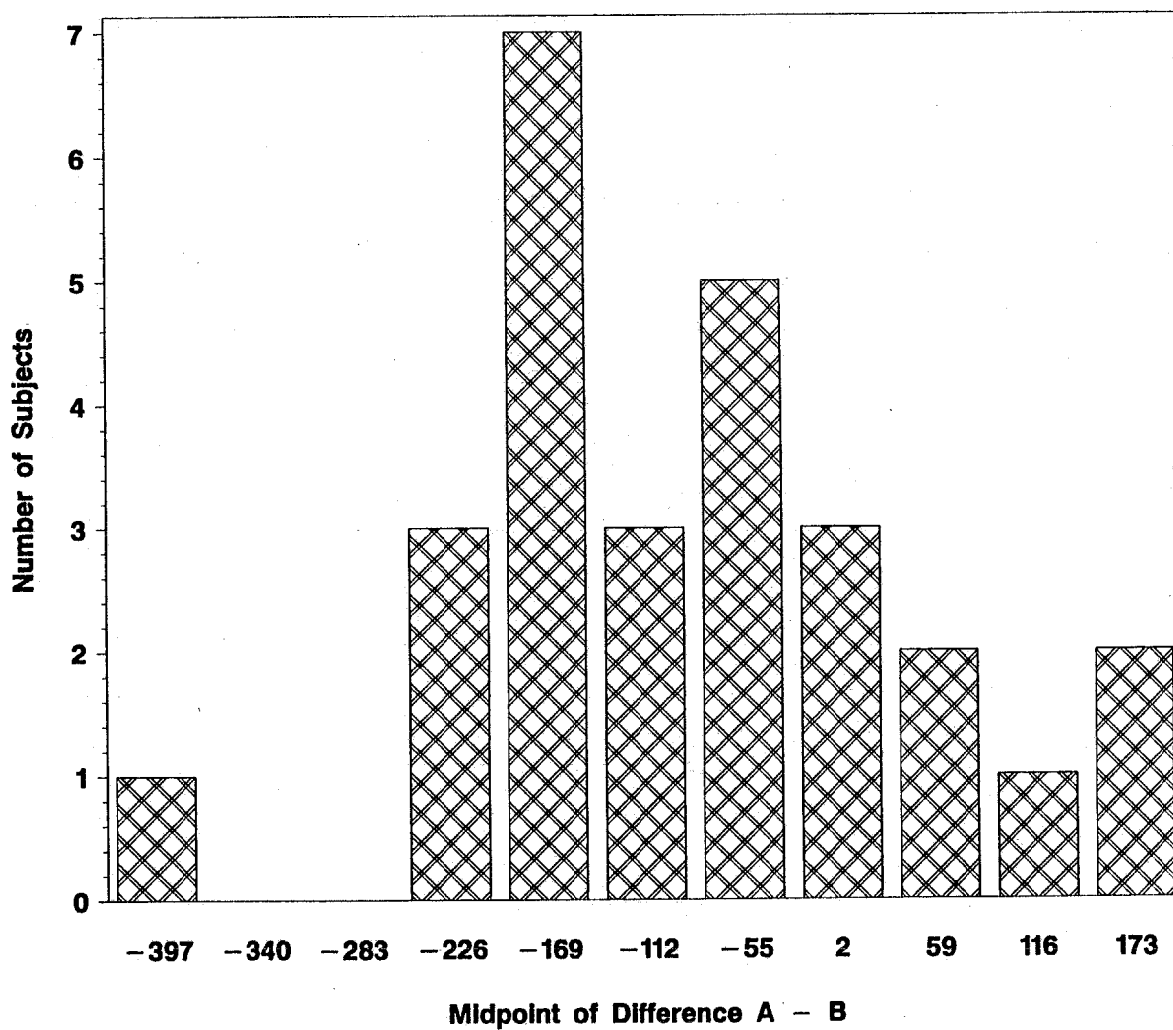


FIGURE 3.A

**Distribution of Ratio of AUC (0-t) Between Formulations for N-DESMETHYLDILTIAZEM
(STUDY # 2443)**

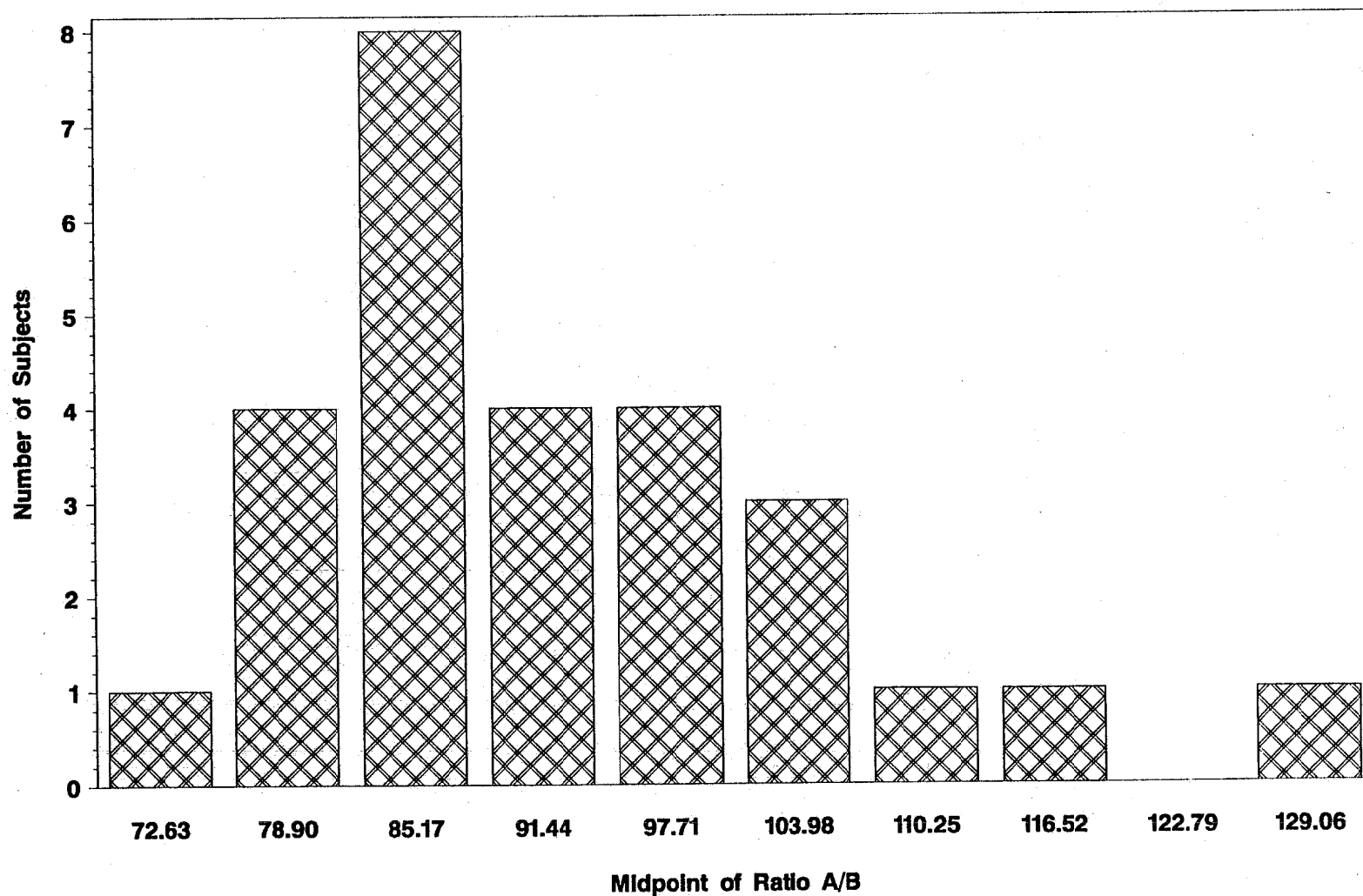


FIGURE 3.B

**Distribution of Difference of AUC (0 - inf) Between Formulations for N-DESMETHYLDILTIAZEM
(STUDY # 2443)**

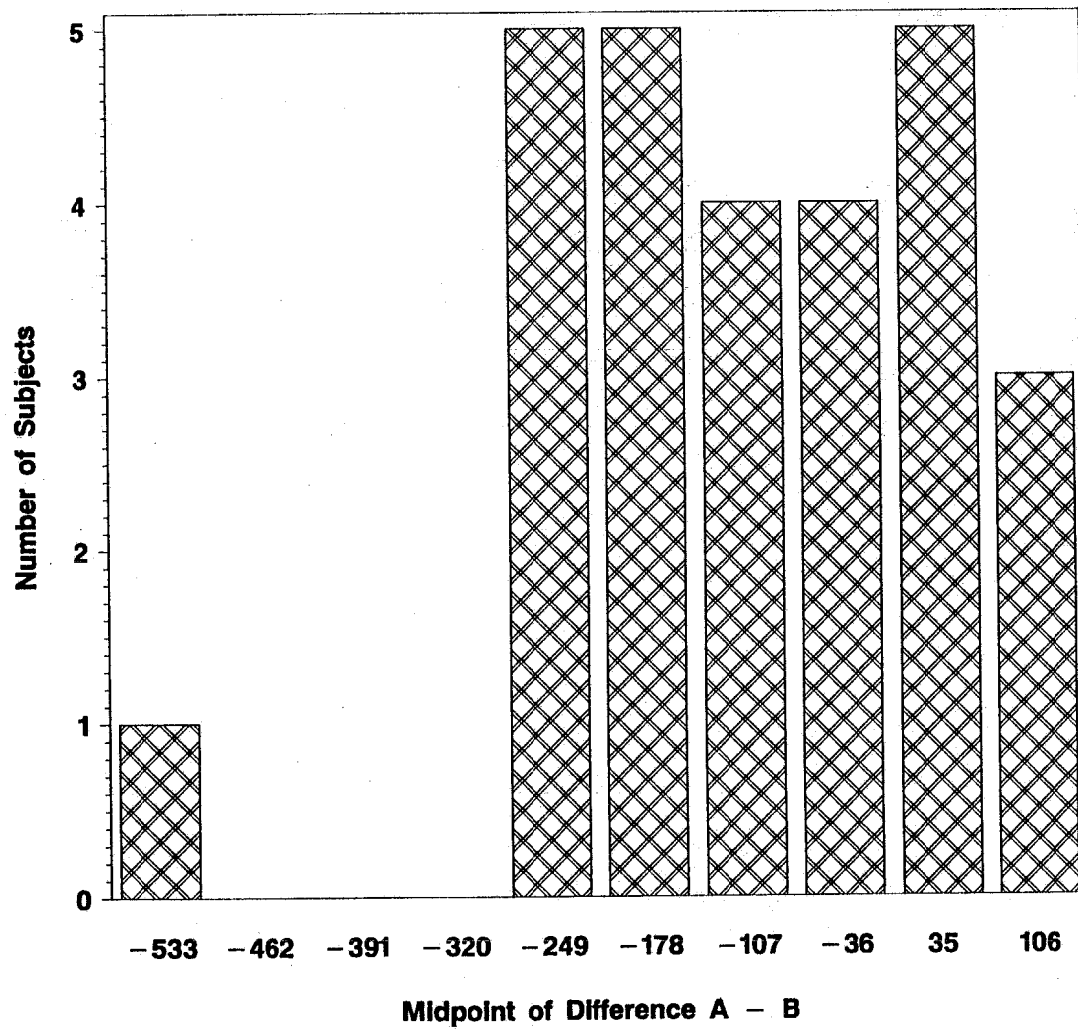


FIGURE 3.C

**Distribution of Ratio of AUC (0 - inf) Between Formulations for N-DESMETHYLDILTIAZEM
(STUDY # 2443)**

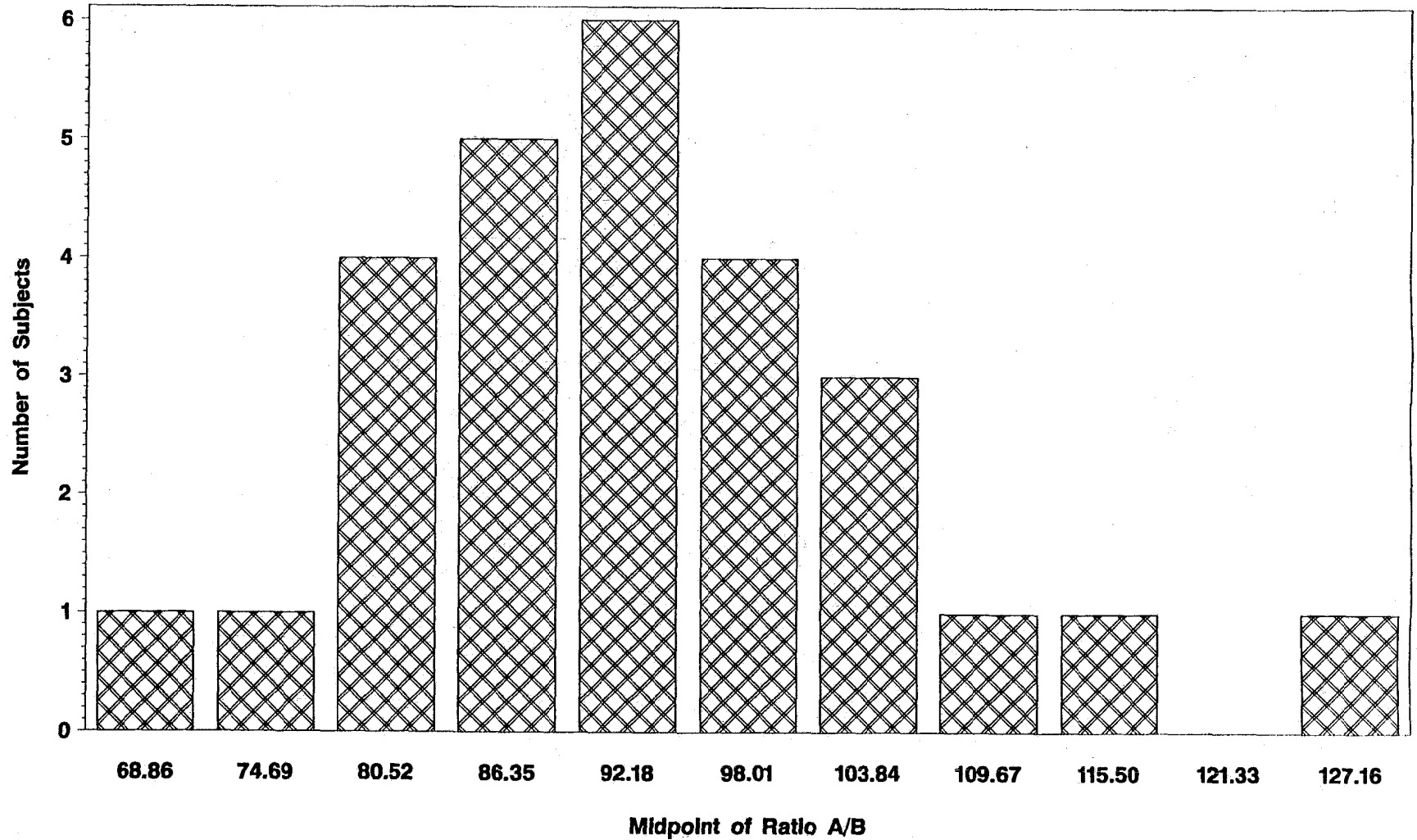


FIGURE 3.D

**Distribution of Difference of Cmax Between Formulations for N-DESMETHYLDILTIAZEM
(STUDY # 2443)**

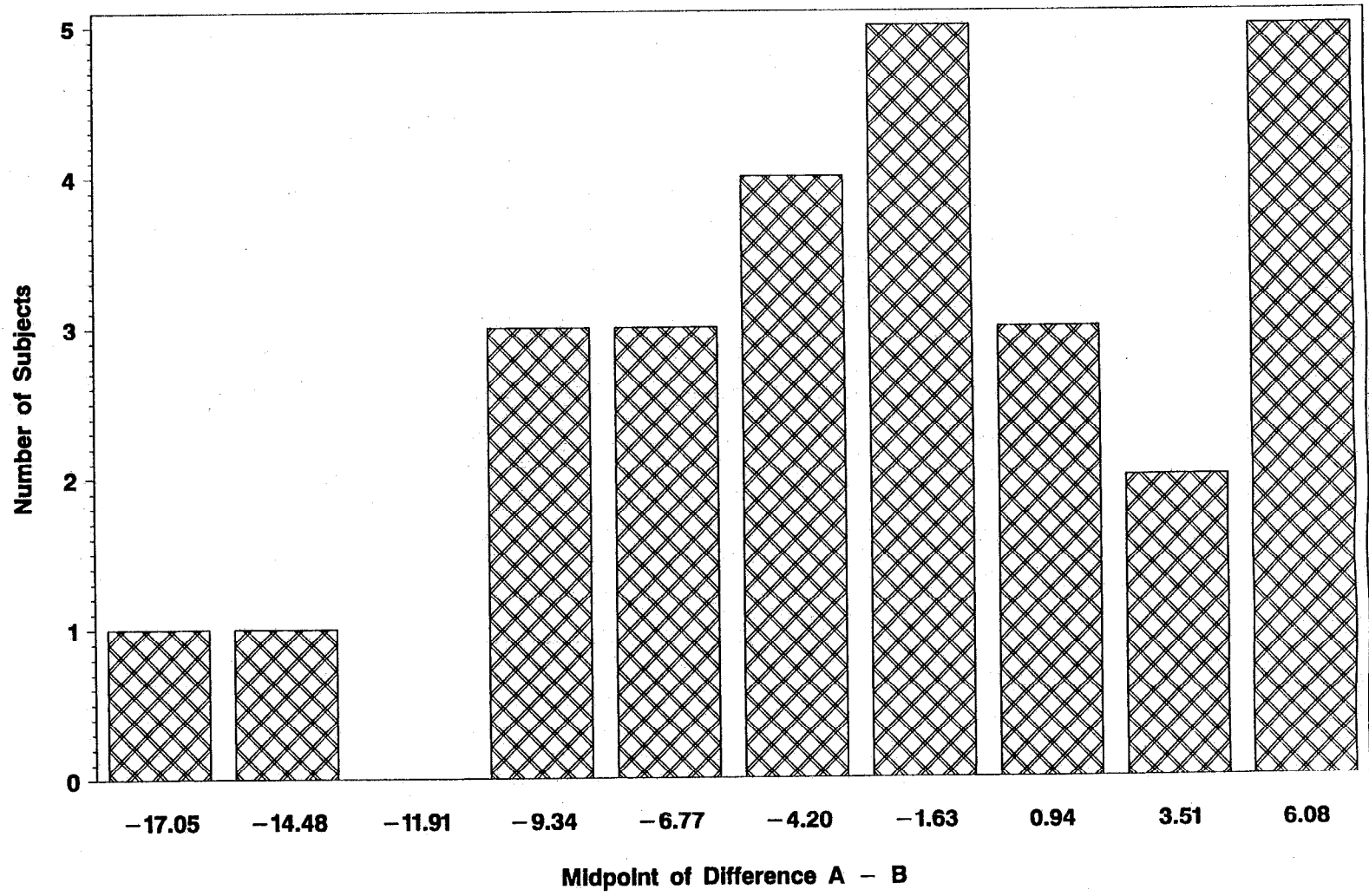


FIGURE 3.E

**Distribution of Ratio of Cmax Between Formulations for N-DESMETHYLDILTIAZEM
(STUDY # 2443)**

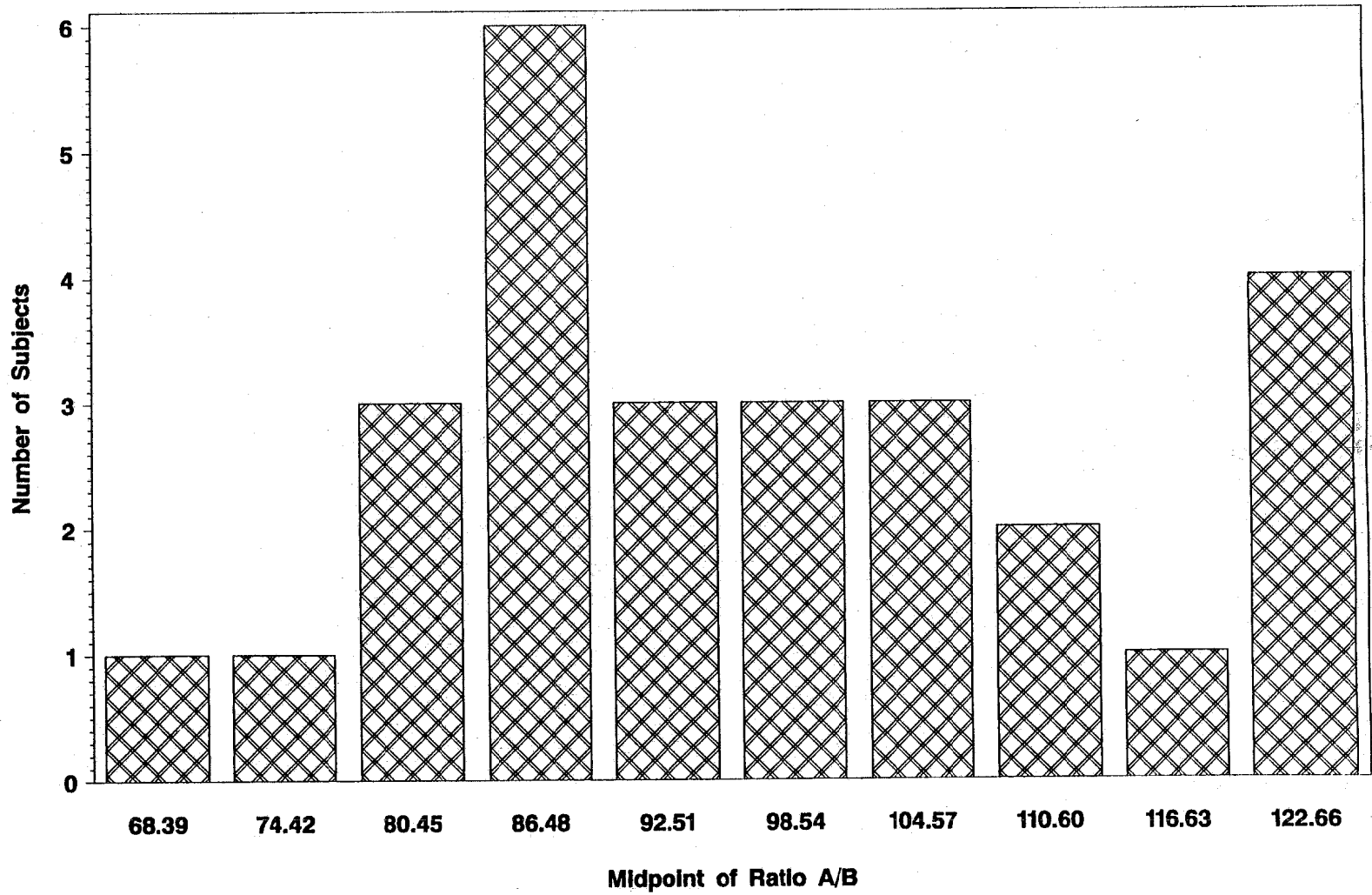


FIGURE 3.F

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS

STUDY # 2443: ALL SUBJECTS IN TEST GROUP

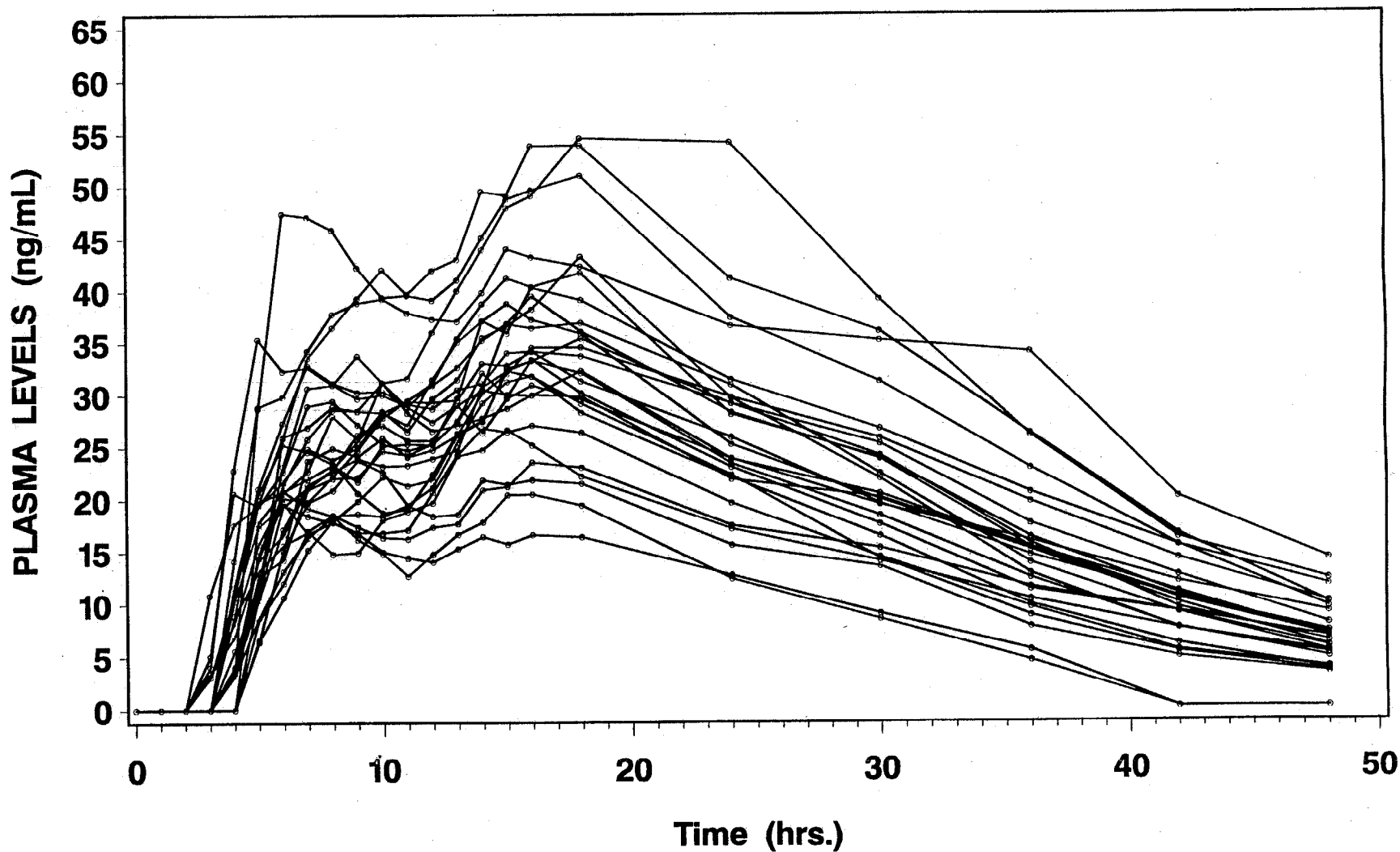


FIGURE 3.84

PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS

STUDY # 2443: ALL SUBJECTS IN REFERENCE GROUP

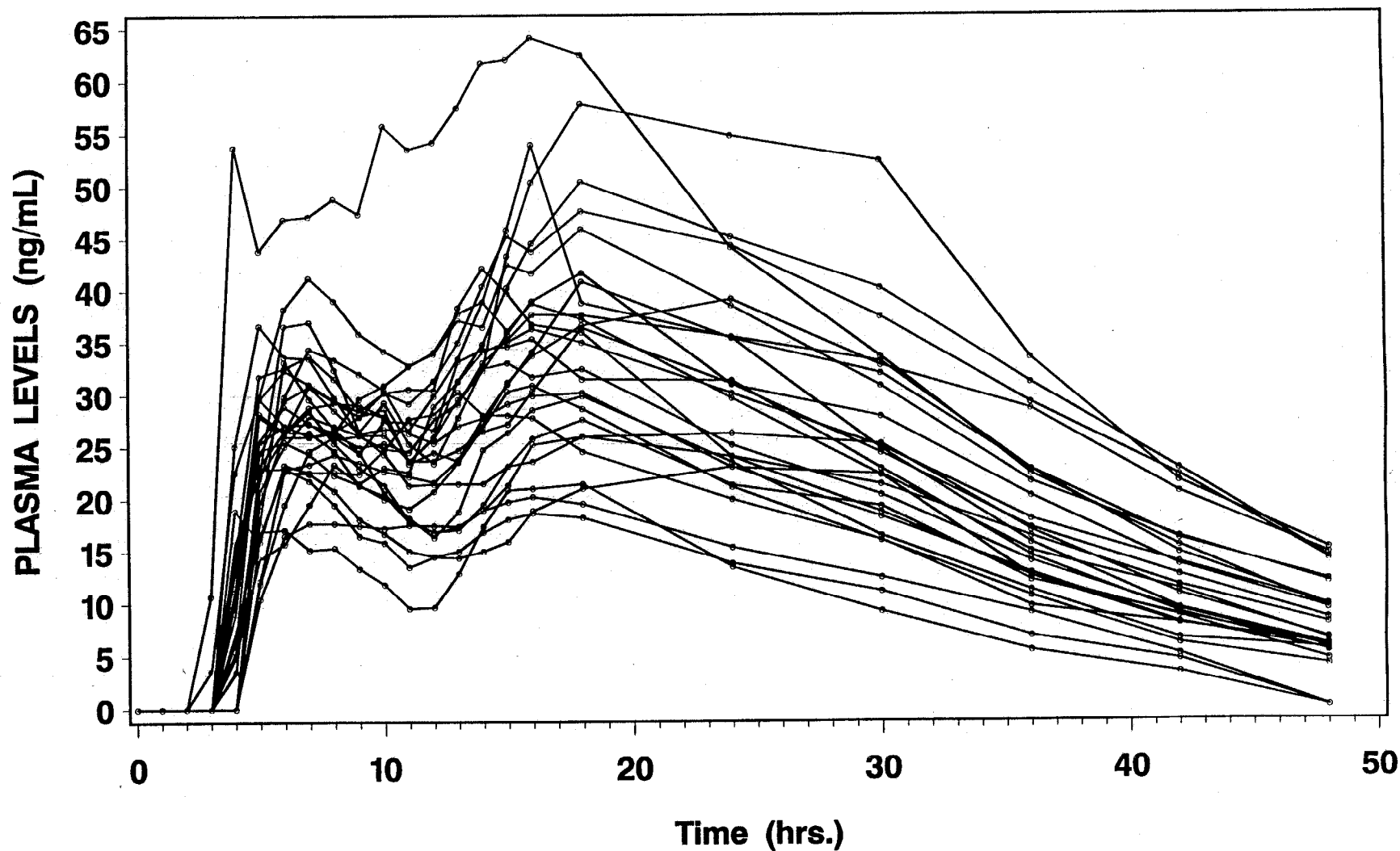


FIGURE 3.85

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS
STUDY # 2443: ALL SUBJECTS IN TEST GROUP

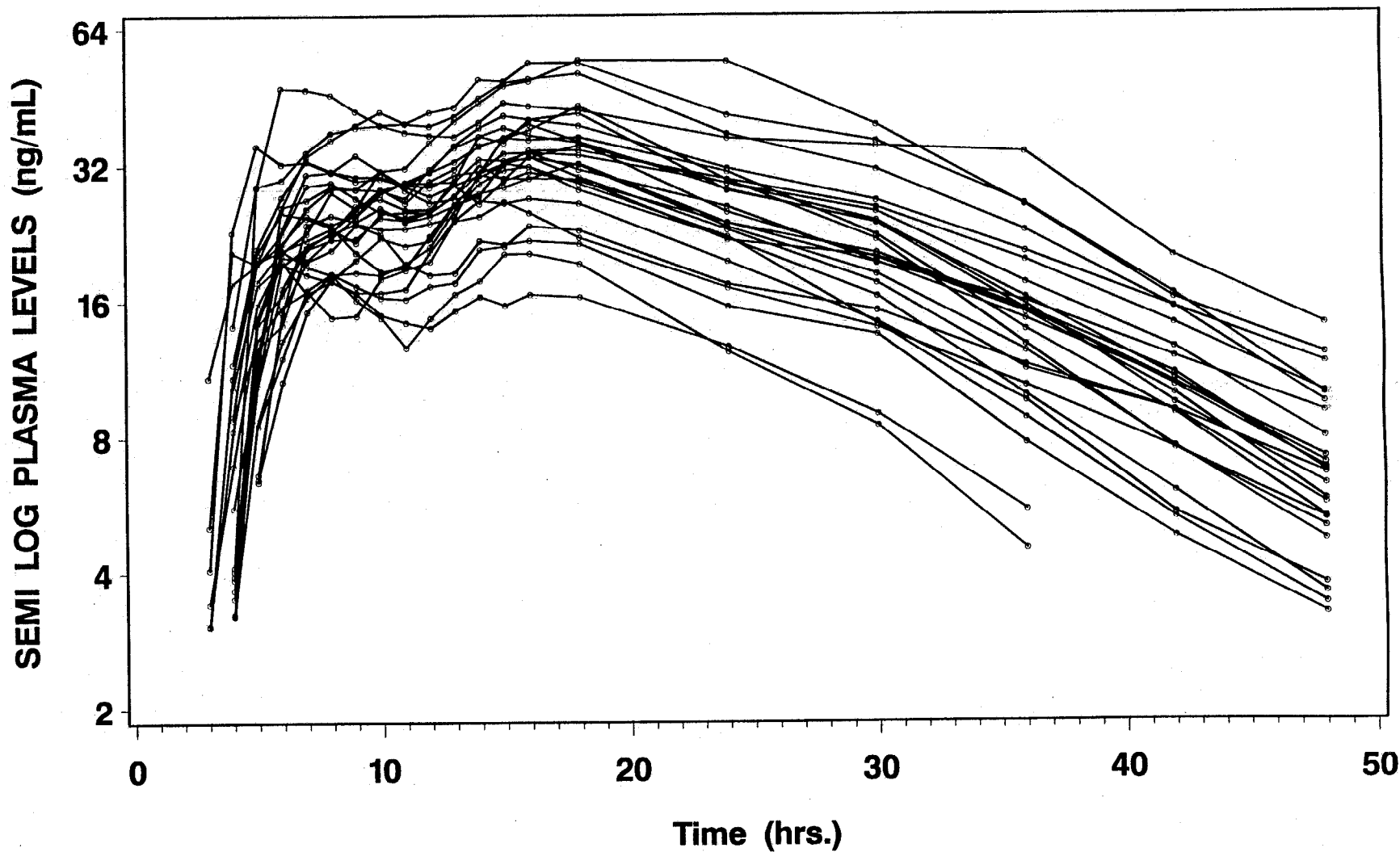


FIGURE 3.86

SEMI LOG PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS

STUDY # 2443: ALL SUBJECTS IN REFERENCE GROUP

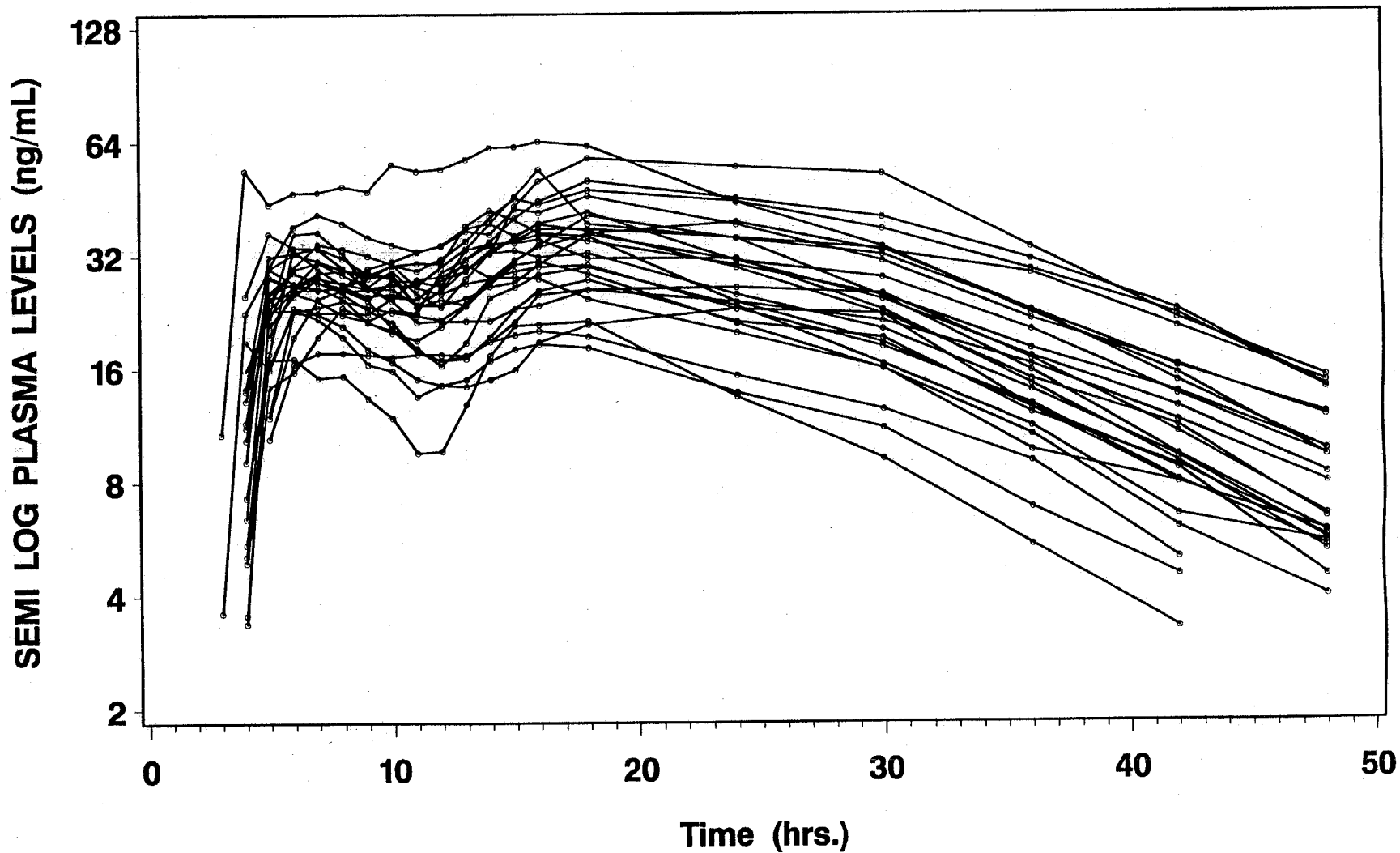


FIGURE 3.87