CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20545

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

110

FEB 29 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 20-545
Type of Submission: Consult with regard to advertisement
Date of Consultation: 02-20-96
Generic name: Procainamide
Brand name: Procanbid
Formulation: ER tablets
Sponsor: Parke-Davis
Reviewer: Olof Borga, Ph.D.

Background: In a letter directed to Dr. Gerald Bunker and dated February 20, 1996, the Division of Drug Marketing, Advertising and Communications (DMAC) has requested that we evaluate some proposed promotional material (appended) for PROCANBID. The following question was asked by DMAC:

"The proposed materials make absolute claims that Procanbid is bioequivalent to Procan SR. Is such a claim a fair and accurate representation? If not, should it be deleted altogether, or would a disclaimer suffice?"

The DMAC also invites other comments that we might have with regard to the promotional material.

Review results: With regard to the specific question asked, the information is accurate. PROCANBID was indeed shown to be bioequivalent to Procan SR when the two drugs were compared with regard to C_{max} and AUC. For details, see my review of the biopharmaceutics portion of NDA 20-545 dated October 13, 1996, on page 7 in the review proper, as well as page 9 (1000-mg Procanbid) and page 14 (500-mg Procanbid) of Appendix 2 of the review.

There is a related statement in the promotional material: "Peak, trough, and average plasma concentrations following twice-daily administration of Procanbid are similar to those achieved with q.i.d. Procan SR." This statement is also accurate.

The mean steady-state plasma concentration curve presented in the material is accurate.

There is a statement made with regard to effect of food on the absorption of procainamide from Procanbid: "Food has a negligible effect on the procainamide absorption when administered twice daily as Procanbid." This statement is also accurate.

FEB 29 1996

Conclusion: The promotional material for Procanbid is accurate with regard to its pharmacokinetic content.

/S/ 2/29/96

Olof Borga, Ph.D. Date
Division of Pharmaceutical Evaluation I

/S/

FT Initialed by Patrick Marroum, Ph.D. 2/29/1996

cc: NDA 20-545, HFD-110 (Willard), HFD-860 (Malinowski, Mehta), HFD-870 (ML Chen), HFD-880 (Fleischer), Drug, FOI (HFD-19), Chron, HFD-340 (Viswanathan).

APPEARS THIS WAY
ON ORIGINAL

BIOPHARMACEUTICS/PHARMACOKINETICS REVIEW

NDA 20-545
Type of Submission: New drug application
Date of Submissions: 12-21-94, 01-19-95, 02-02-95, 02-07-95, 03-06-95, 05-15-95, 08-01-95
Generic name: Procainamide HCl
Brand name: PROCANBID
Formulation: Extended release tablets, 500 and 1000 mg
Sponsor: Parke-Davis, Ann Arbor, MI 48105
Reviewer: Olof Borga, Ph.D.

Synopsis: The Sponsor has developed an extended-release formulation of procainamide (PA), PROCANBID, intended for b.i.d. dosing. Their present formulation, PROCAN SR is dosed q.i.d. The new formulation was accomplished by providing the present wax matrix formulation with a controlled-release coat. The new and the present formulations were bicequivalent in terms of C_{max} and C_{avg} of PA and NAPA during a dosage interval. PROCANBID showed lower C_{min} values than Procan SR, a difference that passed bioequivalence criteria in two studies, but failed in a third. In all three studies PA fluctuations during the dosage interval were larger after PROCANBID. The inter-dose variability, as reflected by trough levels of PA after repeated doses, was low for both formulations, approximately 15-20% CV. Collectively, the data demonstrate a steady-state performance equivalent to that of Procan SR (approved as an ANDA) which has been demonstrated to have a performance equivalent to that of the approved Pronestyl immediate release capsules. Hence, PROCANBID should have a bioperformance equivalent to that of Pronestyl.

A relationship between plasma concentrations of PA and ventricular premature depolarizations (VPD) was tentatively identified using a population kinetics model. The relationship was identical for the old and the new formulation, and further indicated that drug response declines with age. However, the value of this PK-PD analysis was limited by large inter- and intra-subject variability in drug response.

Single doses of the market image 500- and the 1000-mg tablets were dose proportional. Furthermore, dosage strength bioequivalence between the market image 500-mg and 1000-mg tablets was demonstrated, i.e., 2 x 500-mg administered b.i.d. was equivalent to 1 x 1000-mg administered b.i.d. Single dose studies of the two strengths with and without a fat breakfast showed that AUC was significantly increased by food, approximately 15-25%, while C_{max} was essentially unchanged. In conclusion, the Sponsor has demonstrated that the new formulation has acceptable performance. The application is approvable from the Division of Biopharmaceutics' perspective.

TABLE OF CONTENTS

APPENDICES

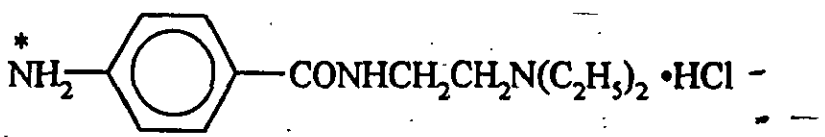
BACKGROUND

Procainamide (PA), a weak organic base, is a Class 1A antiarrhythmic agent with a half-life of the order of 3-4 hours. One major metabolite, N-acetylprocainamide (NAPA) has significant antiarrhythmic activity and a longer half-life than the parent drug, approximately 7 hours. Because of its longer half-life and other potential advantages, it has been tested as an antiarrythmic drug. The acetylation step proceeds with different rates in "fast" and "slow" acetylators, which occur with approximately the same frequency in the US population.

PA is the drug most commonly associated with the induction of autoantibodies and drug-related lupus. Antinuclear antibodies develop faster in slow acetylators of PA, and their development has rarely been seen during therapy with NAPA alone.

Both PA and NAPA are mainly renally excreted. Both glomerular filtration, active tubular secretion, and passive pH-dependent tubular reabsorption occur. The tubular secretion utilizes the base-secreting system also responsible for secretion of metformin, cimetidin, ranitidine, and quinidine. Drug-drug interactions caused by competition for active tubular secretion have been reported. Both PA and NAPA accumulate in patients with impaired renal function.

Drug Substance: Procainamide is a weak organic base with a pK_a of 9.23. The hydrochloride salt used in the present formulation is very soluble in water.



(*Site of acetylation to N-acetylprocainamide)

Drug formulation: The principle for the extended release is a combination of a core consisting of a wax matrix (same as used in Procan SR) and a controlled-release coating. The quantitative compositions of all formulations of PROCANBID used in clinical studies are presented in Tables 1 and 2, side by side with those of Procan SR. Note that all formulations denoted BID except No. 60 were final. Formulation 60 (BID) differed only with respect to the color coat (grey instead of blue).

TABLE 1. Procainamide Hydrochloride 1000-mg Tablet Formulations Tested in Pharmacokinetic and Bioavailability Studies

Formulation No.	46 (BID)	61 (SR)
Tablet Cores		
Procainamide Hydrochloride USP	1000.0	1000.0
Colloidal Silicon Dioxide NF		
Magnesium Stearate NF		
Carnauba Wax FCC		
Polyethylene Glycol 8000 NF		
Weight of Core Tablet		
Controlled-Release Coating		
Hydroxypropyl Cellulose NF		
Simethicone Emulsion USP		
Polyacrylate[a]		
Eudragit NE30D[a]		
Talc USP 400		
Weight After Controlled-Release Coating		
Tablet Coating (Color Coat)		
Opadry Grey YS-1-7507		
Simethicone Emulsion USP		
Weight After Film Coating		
Tablet Polishing		
Candelilla Wax		
Total Tablet Weight		

[a] Added as a dispersion containing % w/w/ solids (Eudragit NE30D)
[b] Does not appear in final product

TABLE 2. Procainamide Hydrochloride 500-mg Tablet Formulations Tested in Pharmacokinetic and Bioavailability Studies

Formulation No.	47 (BID)	59 (SR)	60 (BID)
Tablet Cores			
Procainamide Hydrochloride USP	500.0	500.0	500.0
Colloidal Silicon Dioxide NF			
Magnesium Stearate NF			
Carnauba Wax			
Polyethylene Glycol 8000 NF			
Weight of Core Tablets			
Hydroxypropyl Cellulose NF			
Simethicone Emulsion USP			
Polyethylene Glycol NF 3350			
Polyacrylate[a]			
Talc USP 400			
Weight after Controlled-Release Coating			
Tablet Coating (Color Coat)			
Opadry Grey YS-1-7507			
Opadry Blue YS-5-4295			
Simethicone Emulsion USP			
Weight after Film Coating			
Tablet Polishing			
Candelilla Wax			
Total Tablet Weight			

[a] Added as a dispersion containing % w/w solids (Eudragit NE30D)
[b] Does not appear in final product

Contents of this submission: The development program for PROCANBID has been discussed in four meetings with the firm, the first being held Dec 3, 1987. Normally, the basis for approval of an NDA for an SR-formulation would be to demonstrate that "steady-state performance is equivalent to a currently marketed noncontrolled release or controlled release product" that was subject of a full NDA (CFR 320.25f). Although being a sustained-release formulation, Procan SR, the reference formulation in this application, was approved as an ANDA. However, Procan SR was shown to have a performance equivalent to the approved IR formulation Pronestyl capsule by Squibb. Hence PROCANBID should have a performance equivalent to Pronestyl. The present application also contains a clinical study. Thus the approval of the NDA will not be based on plasma level profiles alone.

Initial attempts to manufacture the market image formulations in were unsuccessful, and manufacturing was transferred to Morris Plains, New Jersey. Three studies using formulations from the site are considered moot. The remaining 9 studies of the submission were reported in the following 10 reports (bioequivalence and PK-PD are reported separately in protocol 610-43, which is also the pivotal clinical study):

Study 1: Bioavailability of PROCANBID 1000-mg tablets as compared to PROCAN SR and the effect of food; a single-dose study.

Study 2: Bioavailability of PROCANBID 500-mg tablets as compared to PROCAN SR and the effect of food; a single-dose study.

Study 3: Relative bioavailability of PROCANBID 1000-mg tablets at steady-state as compared to 500-mg PROCAN SR.

Study 4: Relative bioavailability of 500-mg PROCANBID at steady-state as compared to 500-mg PROCAN SR.

Study 5: Procainamide and NAPA pharmacokinetics as a function of dose and formulation; a multiple-dose study.

Study 6: Evaluation of the relationship between plasma levels and pharmacologic effect.

Study 7: Bioequivalence of PROCANBID 1000-mg tablets at steady-state as compared to formulation used in clinical program.

Study 8: Dose proportionality of market image; a single-dose study.

Study 9: Bioequivalence of PROCANBID 500-mg tablets at steady-state as compared to formulation used in clinical program.

Study 10: Dosage strength bioequivalence between 500- and 1000-mg tablets; a multiple-dose study.

SUMMARY OF PHARMACOKINETICS AND PHARMACODYNAMICS

A detailed review of each pharmacokinetic study is to be found in Appendix 2.

Absorption: Procainamide (PA) appears to be completely absorbed (Graffner et al., Clin Pharmacol Therap 17: 414-423, 1975). First-pass elimination was estimated at 15%. After a conventional tablet, T_{max} occurred within an hour. It appears from studies of extended-release tablets, that the release from the tablet is the rate limiting step in the overall release plus absorption process for PA.

The steady-state performance of PROCANBID administered twice daily was similar to that of Procan SR administered four times daily (Studies 3 and 4). While the two formulations actually were bioequivalent in terms of C_{max} and C_{avg} (average concentration during a dosage interval), C_{min} tended to be lower after PROCANBID. This difference passed bioquivalence criteria in two steady-state studies (Studies 3 and 4) but failed to pass in one study (Study 5). The latter study was geared towards evaluation of PK-PD relationships and undertaken in patients of various ages and renal function. Thus it was not optimal for bioequivalence evaluation. In all three studies, the within-dose variability in PA levels (fluctuation index) was larger after PROCANBID than after Procan SR.

Food studies: The effect of a fat breakfast was evaluated in Study 1 (1000-mg PROCANBID) and Study 2 (500-mg PROCANBID). Using conventional bioequivalence criteria, there was no effect of the meal on C_{max}, while AUC_{∞} was increased by an average 15 to 25%. These results are in line with earlier data on the effect of food on the bioavailability of PA from Procan SR (Rocci et al., Clin Pharmacol Therap 42: 45-49, 1987). These authors concluded that, although the tablet is held up in the stomach for a median time of 3.5 hours (range 1.5-10 hours; data obtained with Heidelberg capsule) by the meal, this did not affect the lag time or T_{max} of PA. Mean AUC increased 30%, while mean C_{max} increased only approximately 8%. The modest effect of the meal with both PROCANBID and Procan SR is probably explained by a dissolution rate that is independent of pH.

Dose proportionality of PROCANBID: In general it appears to be accepted that there exists a dose proportionality for PA *per se*. However, this does not mean that the dose proportionality for the new formulation can be taken for granted. One study to address this issue (Study 5) was not designed as a cross-over study, i.e., each subject was only studied at one dose level. Therefore the more than proportional increase in C_{max}, C_{min}, and C_{avg} when the dose was increased from 1000 mg/day to 2000 mg/day to 4000 mg/day

is difficult to interpret. The recommended daily dose is 2-5 g.

Dose proportionality was demonstrated between single doses of the 500- and the 1000-mg market image tablets (Study 8). The 750-mg tablet gave higher bioavailability than the others, and was eliminated from the development program for this reason.

Dosage strength bioequivalence: The steady-state dosage interval C_{max} and AUC were compared after administration of 2 x 500-mg and 1 x 1000-mg market image tablets (Study 10). The two treatments were shown to be bioequivalent.

Clinical vs market image tablets: The 500-mg tablet used in the clinical multi-center trial was compared with the market image (full-scale production) 500-mg tablet (Study 9). The two formulations were found to be bioequivalent. The 1000-mg clinical and market image tablets were also demonstrated to be bioequivalent (Study 7).

Pharmacokinetics in special populations: No studies in the present submission.

Drug interaction studies: No studies in the present submission.

Gender, age and race effects: The firm's evaluation of steady-state data from Studies 3, 5, 7, 10, and Study Protocol 610-48 (not included in this review; formulation) demonstrated C_{max}, C_{avg}, and C_{min} were approximately one-third larger in women (N=54) than in men (N=45). After normalization for body surface area, mean values were still 20% higher in women. Normalized NAPA concentration data were approximately the same in men and women. Differences between black (N=9) and white (N=90) individuals were negligible. No trend in concentration parameters were observed over the age range (21 to 72 years). The concentration-effect modeling results indicated a decreasing drug response with increasing age; see below.

PK-PD relationship: In Study 6, the Sponsor studied the relationship between the rate at which ventricular premature depolarizations (VPD) occurred and plasma levels of PA and/or NAPA (C_{pa} and C_{NAPA}). Using a population approach and applying mixed effects modeling, various models were tested. However, none of the models provided a consistent explanation of VPD rate as a function of plasma level of PA and/or NAPA. The following inhibitory E_{max} model was the "preferred" model:

$$VPD = 1.25 * AGE * FORM * [1 - C_{pa}/(-3.92 + 0.130*AGE + C_{pa})]$$

Here FORM was 1.99 for PROCAN SR, 2.03 for PROCANBID, and 1.00

for placebo. Since the FORM values found for PROCANBID and PROCAN SR were virtually identical, the model indicates that PA acts identically whether it is released from the old or the new formulation. I_{50} is strongly dependent on age, I_{50} being 0.11 μg/mL at 31 years and 6.2 μg/mL at 78 years. Drug response thus appears to decline with age. The value of this PK-PD analysis was limited by large inter- and intra-subject variability in drug response.

DISSOLUTION METHOD: The method is summarized in the table below.

Dosage Forms:	Tablets
Dose Potencies:	500, 1000 mg
Apparatus:	USP Apparatus II (rotating paddle)
Media:	0-1 hour, 0.1N HCl 1-24 hours, 0.05 M potassium phosphate buffer, pH 7.5
Volume:	900 mL
Agitation:	50 rpm
Temperature:	37°C
Sampling Times:	1, 2, 4, 8, and 24 hours
Analytical Method:	[ ]

Dissolution specifications: The following specifications are recommended. The limits proposed by the firm are given in parentheses:

Time (hours)	Percent Dissolved
1	[ ]
2	
4	
8	
24	

Possible future establishment of an in vitro in vivo correlation might enable the limits to be based on this relationship.

ASSAY: [ ]

Redacted 3

pages of trade

secret and/or

confidential

commercial

information

Labeling Comments

RECOMMENDATION: Upon implementing the suggested labeling changes, the firm's NDA 20-545 is acceptable for approval from the Division of Biopharmaceutics' perspective.

/S/ 10/10/95

Olof Borga, Ph.D. Date
Pharmacokinetics Review Branch

FT Initialed by Ameeta Parekh, Ph.D. /S/ 10/3/95

Biopharm Day: 9/18/95 (Chen, Fleisher, Hepp, Hussain, Lesko, Malinowski, Parekh)

/S/

cc: NDA 20-545, HFD-110, HFD-426 (Fleischer, Borga), HFD-427 (M-L Chen), Drug, FOI (HFD-19), Chron, HFD-340 (Vishwanathan).

APPENDIX 1
REVIEW OF BIOANALYTICAL METHODS

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

APPENDIX 2

REVIEW OF PHARMACOKINETIC STUDIES

Study 1: Bioavailability of PROCANBID 1000-mg tablets as compared to PROCAN SR and the effect of food; a single-dose study.

Study Title: Relative bioavailability of reformulated 1000-mg PROCAN SR BID tablets compared to marketed PROCAN SR tablets as well as the effect of food on the reformulated tablet in healthy volunteers.

Protocol Number: 610-035

Volume Number: 1.9

Objectives: 1) To determine bioavailability relative to a marketed SR-product. 2) To determine the effects of a high-fat meal.

Subjects: Twelve subjects, 8 females and 4 males aged 24 to 44 years (mean 33 years) participated.

Design: Open, single-dose, three-way crossover study.

Treatments: 1) One 1000-mg PROCANBID tablet under fasting conditions.
2) One 1000-mg PROCANBID tablet administered 15 minutes after the start of a fat breakfast. The composition of the breakfast was identical to that recommended by the Division of Biopharmaceutics.
3) One 1000-mg PROCAN SR tablet (marketed); fasting.

In all cases, the tablets were given together with 8 oz of water (fasting) or 8 oz of whole milk (fed).

Formulations: Dissolution profiles were as follows:

Formulation	% Dissolved				
	1 hr	4 hr	6 hr	8hr	12 hr
1000-mg PROCANBID W8213A-46, Lot CM 039028					
1000-mg PROCAN SR W8213-12, Lot No 42667D					

Blood Sampling and Assay: Serial plasma samples were collected for 24 hours and analyzed for PA and NAPA.

Statistical evaluation: The firm had undertaken a statistical evaluation based on untransformed data. For the evaluation of the

effect of the meal only, I repeated the ANOVA and the two one-sided test procedure on the log-transformed AUC_∞ and C_{max} values of procainamide and NAPA. An ANOVA model with sequence, subject (sequence), period, and treatment main effects was used to determine the significance of differences between pharmacokinetic parameter means for each treatment. The confidence intervals reported in the following were obtained with the log-transformed data. My conclusions differ from those of the firm in terms of the extent of bioavailability (AUC_∞) during fasting and fed conditions. The comparison between PROCANBID and PROCAN SR was not reevaluated using log-transformed data, since a single-dose comparison with the present design was not considered conclusive (see below).

STUDY RESULTS:

Comparison of PROCANBID and PROCAN SR: The mean apparent $t_{\frac{1}{2}}$ was different during the two treatments: 9.1 hours after PROCANBID and 4.9 hours after PROCAN SR. This indicates ongoing absorption for PROCANBID during the presumed elimination phase, which casts doubt whether the present study design gives an accurate estimate of the relative bioavailabilities. A design using multiple doses, and a comparison of the steady-state dosage intervals would be preferable. Nevertheless, based on AUC_∞ ratios, the present study estimates the bioavailability of PROCANBID as, on the average, 93% of that of PROCAN SR.

Effect of a meal: While T_{max} of procainamide showed a significant increase (by approximately 44%), the mean plasma concentration curve for procainamide after a fat meal actually differed only slightly from that during fasting conditions (see Figure 1a). In terms of C_{max}, the two conditions were bioequivalent (see Table 1). The same was true for C_{max} of NAPA (see Figure 1b and Table 2).

In terms of extent (AUC_∞) of procainamide, the two conditions were not bioequivalent using the log-transformed data or (~~in~~ spite of claims by the firm to the contrary) did not pass using nontransformed data either. However, the difference during the two prandial conditions was quite small (+15% after the meal) and should be of little clinical concern (see Table 1). In terms of AUC_∞ of NAPA the two conditions were in fact bioequivalent (see Table 2).

Table 1. Pharmacokinetic parameters for procainamide, mean (%CV), after administration of a 1000-mg PROCANBID tablet to 11 healthy subjects during fasting and fed conditions.

Condition	AUC_∞ (mg*hr/L)	C_{max} (mg/L)	T_{max} (hr)
Fasted	18.9 (29%)	1.35 (27%)	3.9 (20%)
Fed	21.8 (22%)	1.38 (29%)	5.6 (30%)
Ratio Fed/Fasted	1.15	1.02	1.44
Confidence Interval	103.7-133.3	94.8-110.5	-

Table 2. Pharmacokinetic parameters for NAPA, mean (%CV), after administration of a 1000-mg PROCANBID tablet to 11 healthy subjects during fasting and fed conditions.

Condition	AUC_t (mg*hr/L)	C_{max} (mg/L)	T_{max} (hr)
Fasted	10.3 (38%)	0.61 (41%)	7.8 (51%)
Fed	11.4 (46%)	0.67 (48%)	12.3 (34%)
Ratio Fed/Fasted	1.11	1.10	1.58
Confidence Interval	97.5-116.8	97.7-114.7	-

Conclusions: 1) After a high-fat meal, the composition of which was in accordance to the guidelines of the Division of Biopharmaceutics, the bioavailability (AUC_∞) of procainamide after a PROCANBID 1000-mg tablet increased only moderately (approximately %) while C_{max} was unchanged. Changes in NAPA parameters were insignificant.

2) Tentatively, the relative bioavailability of the new formulation, 1000-mg PROCANBID, was estimated at % of that of the marketed formulation, 500-mg PROCAN SR. Definite conclusions would have have to await a multiple-dose comparison.

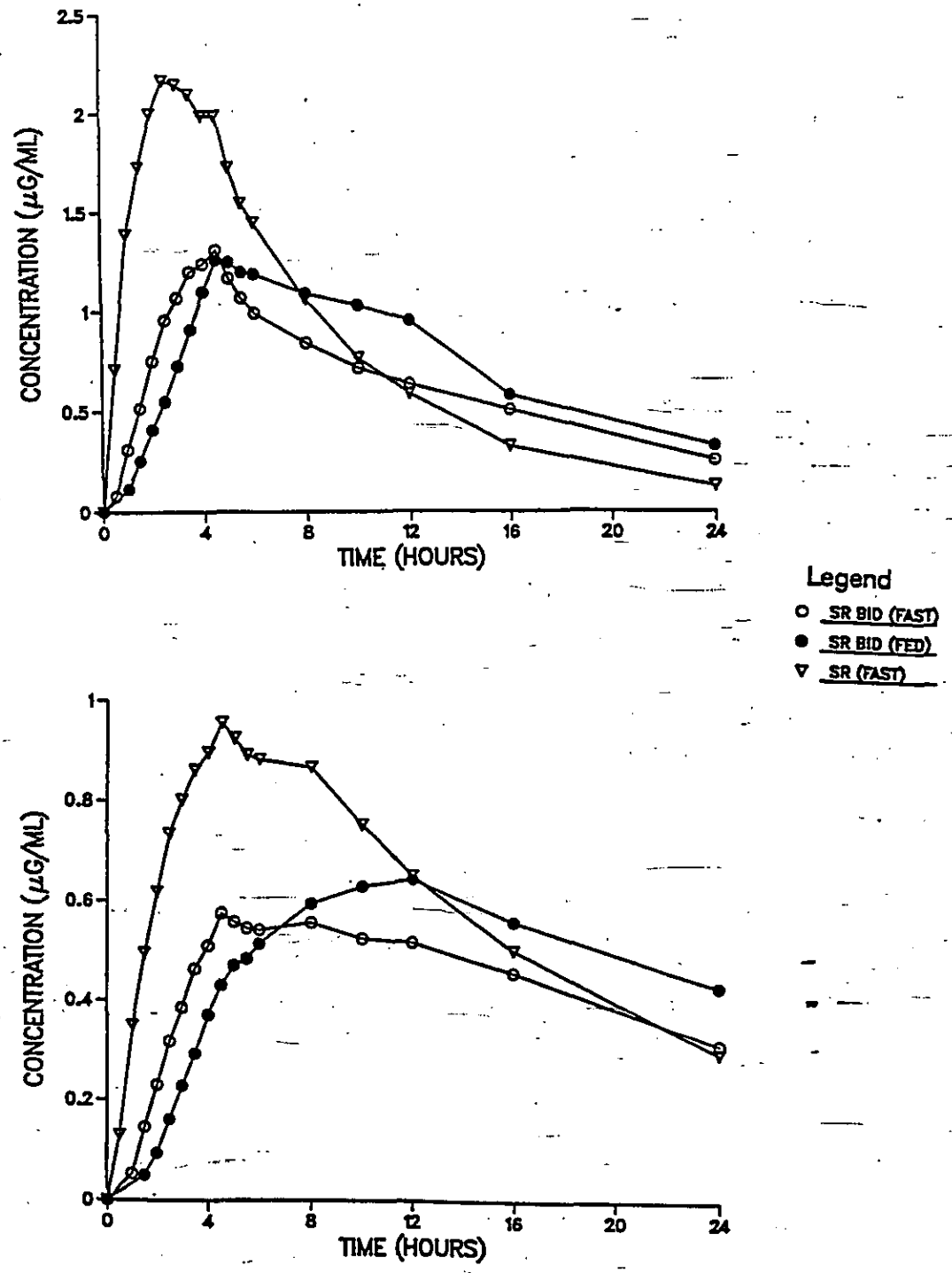


Figure 1. Mean concentrations of a) procainamide (top) and b) NAPA (bottom) in 11 healthy subjects following administration of a single dose of 1000-mg PROCANBID during fasted and fed conditions and PROCAN SR during fasted conditions.

Study 2: Bioavailability of PROCANBID 500-mg tablets as compared to PROCAN SR and the effect of food; a single-dose study.

Study Title: Relative bioavailability of reformulated 500-mg PROCAN SR BID tablets compared to marketed 500-mg PROCAN SR tablets and the effect of food on the reformulated tablets in healthy volunteers.

Protocol Number: 610-038

Volume Number: 1.10

Objectives: 1) To determine bioavailability relative to a marketed SR-product. 2) To determine the effects of a high-fat meal.

Subjects: Eleven subjects, 5 females and 6 males aged 23-44 years (mean 33 years) participated.

Design: Open, single-dose, three-way crossover study.

Treatments: 1) Two 500-mg PROCANBID tablets under fasting conditions.
2) Two 500-mg PROCANBID tablet administered 15 minutes after starting a high-fat breakfast. The composition of the breakfast was identical to that recommended by the Division of Biopharmaceutics.
3) Two 500-mg PROCAN SR tablet (marketed) under fasting conditions.

In the fasting condition, the tablets were given together with 8 oz of water. In the fed condition, the tablets were given together with a portion of the milk.

Formulations: PROCANBID was manufactured at while PROCAN SR was manufactured at Dissolution profiles were as follows:

Formulation	% Dissolved				
	1 hr	4 hr	6 hr	8hr	12 hr
500-mg PROCANBID W8213A-47 Lot CM 163068					
500-mg PROCAN SR Lot No 041D7VA					

Blood Sampling and Assay: Serial plasma samples were collected for 24 hours and analyzed for PA and NAPA.

Statistical evaluation: The firm had undertaken a statistical evaluation based on untransformed data. For the evaluation of the effect of the meal only, I repeated the ANOVA and the two one-sided test procedure on the log-transformed AUC_∞ and C_{max} values of procainamide and NAPA. An ANOVA model with sequence, subject (sequence), period, and treatment main effects was used to determine the significance of differences between pharmacokinetic parameter means for each treatment. While the overall conclusions did not change from those of the firm, the confidence intervals reported in the following were obtained with the log-transformed data. The comparison between PROCANBID and PROCAN SR was not reevaluated using log-transformed data, since a single-dose comparison with the present design was not considered conclusive (see below).

STUDY RESULTS:

Effect of a meal: The meal tended to delay the absorption slightly (see Table 1 below). For the parent drug, the AUC_∞ was increased by approximately %, while C_{max} was virtually unchanged. Based on the confidence interval for AUC_∞, one may conclude that fed and fasted conditions are not bioequivalent. In contrast, the data for NAPA (summarized in Table 2 below) were bioequivalent during fasted and fed conditions.

Table 1. Pharmacokinetic parameters for procainamide, mean (%CV), after administration of PROCANBID to 11 healthy subjects during fasting and fed conditions.

Condition	AUC_∞ (mg*hr/L)	C_{max} (mg/L)	T_{max} (hr)
Fasted	19.1 (37%)	1.69 (26%)	4.3 (40%)
Fed	23.8 (30%)	1.76 (32%)	5.1 (14%)
Ratio Fed/Fasted	1.25	1.04	1.19
Confidence Interval	113.5-142.7	93.5-117.9	-

Table 2. Pharmacokinetic parameters for NAPA, mean (%CV), after administration of PROCANBID to 11 healthy subjects during fasting and fed conditions.

Condition	AUC_t (mg*hr/L)	C_{max} (mg/L)	T_{max} (hr)
Fasted	10.8 (39%)	0.65 (35%)	6.4 (28%)
Fed	11.0 (39%)	0.65 (40%)	10.5 (24%)
Ratio Fed/Fasted	1.02	1.00	1.64
Confidence Interval	92.1-113.6	89.0-110.2	-

Comparison of 500-mg PROCANBID and 500-mg PROCAN SR: The data for PROCANBID indicates that absorption may be ongoing beyond the 24-hour sampling period. Thus, this single-dose comparison may underestimate the relative bioavailability of PROCANBID in relation to PROCAN SR. A more relevant comparison would be to measure AUC of the dosage interval after multiple doses. Nevertheless, the present comparison of procainamide AUC_∞ of the two formulations indicate that the bioavailability of PROCANBID is approximately % of that of PROCAN SR.

Conclusion: 1) After a fat-breakfast (composition in accordance with the guidelines of the Division of Biopharmaceutics) the bioavailability of procainamide after a 500-mg PROCANBID tablet is increased by approximately %. Changes in the bioavailability of NAPA were insignificant.

2) Tentatively, the relative bioavailability of the new formulation, 500-mg PROCANBID, was estimated at % of that of the marketed formulation, 500-mg PROCAN SR. Definite conclusions would have have to await a multiple-dose comparison.

Study 3: Relative bioavailability of PROCANBID 1000-mg tablets at steady-state as compared to 500-mg PROCAN SR.

Study Title: Steady-state bioavailability of reformulated 1000-mg PROCAN SR BID tablets relative to that of marketed 500-mg PROCAN SR tablets: Protocol 610-39

Protocol Number: 610-039

Volume Number: 1.11

Objectives: To determine bioavailability relative to that of marketed 500-mg Procan SR tablets during multiple doses.

Subjects: Eighteen healthy subjects were recruited and 15 completed the study. Of these 6 were females and 9 males. The ages ranged from 23 to 41 years (mean 32 years).

Design: Open, randomized, multi-dose, two-way crossover study.

Treatments: 1) One 1000-mg PROCANBID tablets every twelve hours for seven doses.
2) One 500-mg PROCAN SR tablet (marketed) every six hours for 14 doses.

Formulations: Dissolution profiles were as follows:

Formulation	% Dissolved				
	1 hr	4 hr	6 hr	8hr	12 hr
1000-mg PROCANBID W8213A-46, Lot CM 039028					
500-mg PROCAN SR Lot No 02458VB					

Blood Sampling and Assay: Plasma samples were collected before dose, and 24, 48, 60, and serially from 72 hours to 84 hours after the initial dose of each treatment. Samples were analyzed for PA and NAPA.

Statistical evaluation: The firm had undertaken a statistical evaluation based on untransformed data. An ANOVA model with sequence, subject (sequence), period, and treatment main effects had been used to determine the significance of differences between pharmacokinetic parameter means for the two treatments. The comparison between PROCANBID and PROCAN SR was not reevaluated using log-transformed data, since the outcome was not likely to be different using log-transformed data. Furthermore, there is no absolute regulatory requirement of bioequivalence in

the present situation.

STUDY RESULTS:

Comparison of performance at steady-state: The mean steady-state plasma concentration curves for procainamide and NAPA are presented in Figure 1. In general, the C_{max} values were similar for the two formulations, while C_{min} was lower for PROCANBID. As a concequence, the "fluctuation index", $(C_{max} - C_{min})/C_{min}$ was greater for PROCANBID. This and results of other comparisons, such as AUC(72-84hr), plus the 90% confidence intervals, are reported in Tables 1 and 2 for procainamide and NAPA, respectively.

Table 1. Pharmacokinetic parameters for procainamide, mean (%CV), during steady-state following multiple doses of 1000-mg PROCANBID and 500-mg PROCAN SR tablets.

Parameter	PROCANBID	PROCAN SR	Test/Ref	90% Confidence interval
C_{max} (mg/L)	2.64 (32%)	2.72 (30%)	0.97	94-101
T_{max} (hr)	3.9 (23%)	1.9 (38%)	2.05	-
AUC(72-84) (mg*hr/L)	24.0 (36%)	26.1 (32%)	0.92	87-96
C_{min} (mg/L)	1.40 (38%)	1.58 (35%)	0.89	81-95
$(C_{max} - C_{min})/C_{min}$	0.95 (41%)	0.76 (30%)	1.25	101-155

The first thing worth noting is that the ratio of the two active moieties, procainamide and NAPA, is virtually unchanged with the new formulation (compare for instance AUCs). Thus, while the absorption of the new formulation most likely utilizes a more distal part of the GI tract, this circumstance has obviously not caused any change in the extent of first-pass metabolism of procainamide to NAPA.

The second thing that is worth noting is that, on the basis of assay content, the actual 1000-mg PROCANBID dose was % less than that given as 500-mg PROCAN SR. Taking this into account will eliminate a fairly large part of the apparent differences in AUC(72-84) and C_{min}. However, it will not change the fact that the variation in plasma levels during a dosage interval is larger with the new formulation as compared to the marketed.

Table 2. Pharmacokinetic parameters for NAPA, mean (%CV), during steady-state following multiple doses of 1000-mg PROCANBID and 500-mg PROCAN SR tablets.

Parameter	PROCANBID	PROCAN SR	Test/Ref	90% Confidence interval
C_{max} (mg/L)	1.56 (53%)	1.78 (54%)	0.88	81-95
T_{max} (hr)	4.7 (33%)	3.0 (28%)	1.57	
AUC(72-84) (mg*hr/L)	17.0 (54%)	19.2 (55%)	0.89	81-96
C_{min} (mg/L)	1.23 (56%)	1.41 (55%)	0.87	80-95
$(C_{max} - C_{min})/C_{min}$	0.30 (43%)	0.27 (27%)	1.11	86-140

Dose-to-dose variability: According to CFR 320.25 (e) a controlled release formulation should, among other things meet the following requirement: "The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units." Since this was not addressed in the present study, I undertook a comparison of the trough concentrations of PA and NAPA at 48, 60, 72, and 84 hours of repeated administration of the two formulations: Mean and % rel.SD were calculated for each individual and formulation. Table 3 summarizes the average data for all subjects.

Table 3. Mean inter-dose variability in predose plasma concentration of procainamide and NAPA.

	PROCANBID	PROCAN SR
Procainamide	14.7%	11.7%
NAPA	10.0%	7.4%

The inter-dose variability of parent drug and active metabolite was low for both formulations. Thus the performance of PROCANBID 1000-mg tablet seems to be consistent from dose to dose.

Conclusions: The new formulation, PROCANBID 1000-mg tablet, will, when administered twice daily, result in a dosage interval AUC similar to that of the marketed formulation, PROCAN SR 500-mg tablet, administered four times daily.

The variation of the plasma level within the dosage interval will be slightly higher with the new formulation.

An acceptable dose-to-dose performance of PROCANBID 1000-mg tablet has been demonstrated.

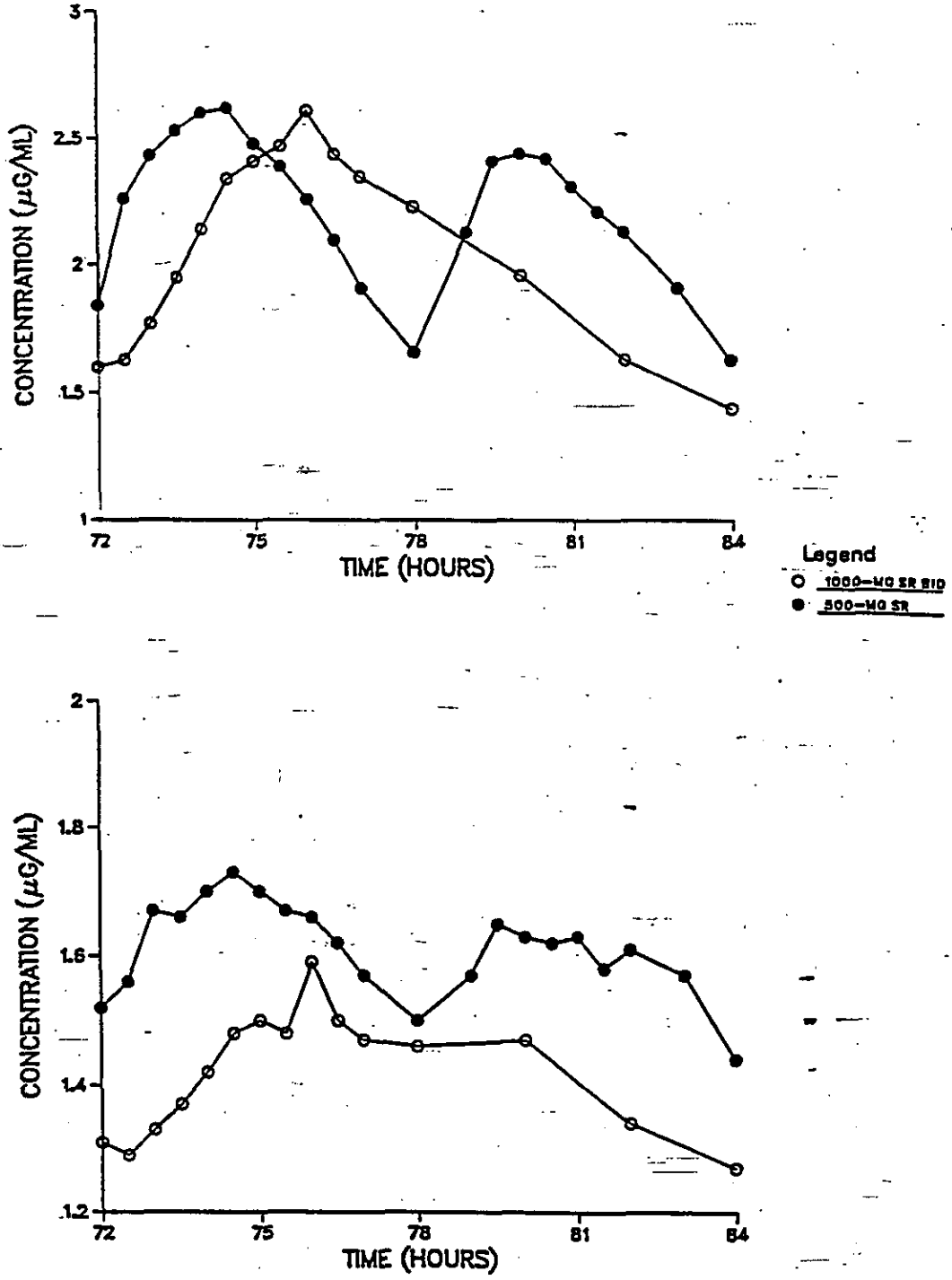


Figure 1. Mean plasma concentration profiles for procainamide (top) and NAPA (bottom) following multiple-dose administration of 1000-mg PROCANBID or 500-mg PROCAN SR tablets (protocol 610-39). N.b. that the axes don't intersect in the origin.

Study 4: Relative bioavailability of 500-mg PROCANBID at steady-state as compared to 500-mg PROCAN SR.

Study Title: Steady-state bioavailability of 500-mg PROCAN SR BID tablets relative to that of marketed 500-mg PROCAN SR tablets: Protocol 610-40

Study Number: RR-764-01257

Volume Number: 1.12

Objectives: To determine bioavailability relative to that of marketed 500-mg Procan SR tablets during multiple doses.

Subjects: Eighteen healthy subjects took part in the study. Of these, 10 were females and 8 were males. The ages ranged from 19 to 43 years (mean 31 years).

Design: Open, randomized, multi-dose, two-way crossover study.

Treatments: 1) Two 500-mg PROCANBID tablets (W8213A-47) every twelve hours for seven doses.
2) One 500-mg PROCAN SR tablet (marketed, Lot No 02458VB) every six hours for 14 doses.

Formulations: Dissolution profiles were as follows:

Formulation	% Dissolved				
	1 hr	4 hr	6 hr	8hr	12 hr
500-mg PROCANBID W8213A-47, Lot CM-163068					
500-mg PROCAN SR Lot No 02458VB					

Blood Sampling and Assay: Plasma samples were collected before, 24, 48, 60, and serially from 72 hours to 84 hours after the initial dose of each treatment. Samples were analyzed for PA and NAPA.

Statistical evaluation: The firm had undertaken a statistical evaluation based on untransformed data. An ANOVA model with sequence, subject (sequence), period, and treatment main effects had been used to determine the significance of differences between pharmacokinetic parameter means for the two treatments. The comparison between PROCANBID and PROCAN SR was not reevaluated using log-transformed data, since the outcome was not likely to be different using log-transformed data. Furthermore,

there is no absolute regulatory requirement of bioequivalence in the present case.

STUDY RESULTS:

Comparison of performance at steady-state: The mean steady-state plasma concentration curves for procainamide and NAPA are presented in Figure 1. The pharmacokinetic parameters of interest are listed in Table 1 for procainamide and Table 2 for NAPA. Mean C_{max} for procainamide was similar for the two formulations (see Table 1) while C_{min} was considerably lower for the new formulation. As noted with the 1000-mg PROCANBID tablet, the "fluctuation index", $(C_{max} - C_{min})/C_{min}$, was larger with the new 500-mg formulation. In fact, the within-dose performance of the 500-mg PROCANBID was considerably larger than for the 1000-mg PROCANBID. AUC(72-84) was slightly lower for PROCANBID, corresponding to a relative bioavailability of %. This decrease was also reflected in NAPA values (Table 2).

Table 1. Pharmacokinetic parameters for procainamide, mean (%CV), during steady-state following multiple doses of 2x500-mg PROCANBID and 500-mg PROCAN SR tablets.

Parameter	PROCANBID	PROCAN SR	Test/Ref	90% Confidence interval
C_{max} (mg/L)	2.62 (18%)	2.74 (20%)	0.96	88-103
T_{max} (hr)	3.6 (28%)	1.9 (29%)	1.89	-
AUC(72-84)	22.6 (20%)	25.6 (21%)	0.88	81-95
C_{min} (mg/L)	1.16 (31%)	1.44 (23%)	0.81	-72-88
$(C_{max} - C_{min})/C_{min}$	1.53 (71%)	0.96 (38%)	1.59	120-201

Table 2. Pharmacokinetic parameters for NAPA, mean (%CV), during steady-state following multiple doses of 2x500-mg PROCANBID and 500-mg PROCAN SR tablets.

Parameter	PROCANBID	PROCAN SR	Test/Ref	90% Confidence interval
C_{max} (mg/L)	1.76 (39%)	2.05 (42%)	0.86	79-93
T_{max} (hr)	3.4 (28%)	2.9 (47%)	1.17	-
AUC(72-84) (mg*hr/L)	18.6 (40%)	21.4 (43%)	0.87	80-94
C_{min} (mg/L)	1.27 (43%)	1.48 (39%)	0.86	81-90
$(C_{max} - C_{min})/C_{min}$	0.42 (48%)	0.39 (48%)	1.08	88-126

Day-to-day variability: As in Study 3, I compared the variability of predose plasma levels of procainamide and NAPA between the two formulations:

Table 3. Mean interdose variability in predose plasma concentration of procainamide and NAPA.

	PROCANBID	PROCAN SR
Procainamide	19.4%	13.4%
NAPA	11.3%	7.2%

As was found for the 1000-mg PROCANBID tablet, the dose-to-dose performance of the 500-mg PROCANBID tablet was acceptable.

Conclusions: The new formulation, PROCANBID 500-mg tablet, will, when two tablets are being administered twice daily, result in a dosage interval AUC similar to that of the marketed formulation, PROCAN SR 500-mg tablet, administered four times daily. The relative bioavailability of the new, as compared to the existing, formulation was estimated at %.

The variation of the plasma level within the dosage interval will be slightly higher with the new formulation.

An acceptable dose-to-dose performance of PROCANBID 500-mg tablet has been demonstrated.

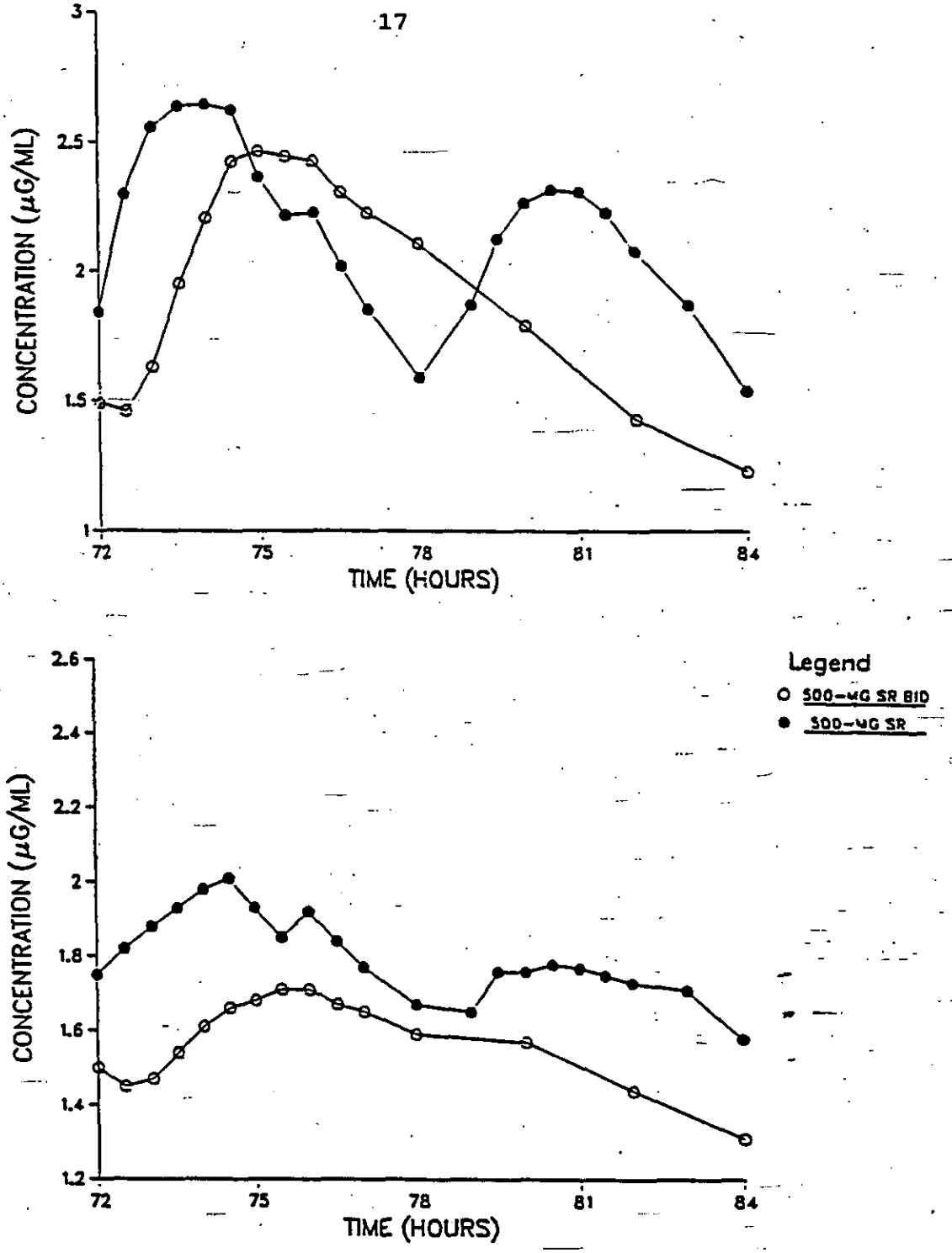


Figure 1. Mean plasma concentration profiles for procainamide (top) and NAPA (bottom) following multiple-dose administration of 2x500-mg PROCANBID b.i.d. or 500-mg PROCAN SR tablets q.i.d. (protocol 610-40). N.b. that the axes don't intersect in the origin.

Study 5: Procainamide and NAPA pharmacokinetics as a function of dose and formulation; a multiple-dose study.

Study Title: A double-blind, parallel-group, formulation-crossover, placebo-controlled, multicenter study comparing the activity of a new formulation of procainamide administered bid to suppress ventricular premature depolarizations.

Study Number: RR-764-02031

Volume Number: 1.13

Objectives: To evaluate procainamide and NAPA (N-acetylprocainamide) pharmacokinetics as a function of dose and treatment. The other objective, to evaluate the relationship between drug plasma levels and effect, is presented in Study 6.

Design: A 1-week wash-out followed by a 2-week double-blind formulation-crossover treatment. Patients were randomized to 1 of 4 dose levels (see following table) and to either the Procan SR (QID) formulation or PROCANBID in the first week. Maintaining the dose, they were then crossed over to the alternative formulation in the second week without a washout between treatments.

Dose Level (mg/day)	Sequence	Period 1	Period 2
0 (placebo)	A	QID	BID
	B	BID	QID
1000	C	QID	BID
	D	BID	QID
2000	E	QID	BID
	F	BID	QID
4000	G	QID	BID
	H	BID	QID

Treatments: Study medications were Procan SR 250-mg, 500-mg, 1000-mg, and placebo tablets, and procainamide BID 500-mg, 1000-mg, and placebo tablets all manufactured in [redacted] (In the submission it was stated that site of manufacture was [redacted] When questioned about this, the firm states that this was an error).

	% Dissolved			
Procan SR	1 hr	4 hr	8 hr	12 hr
250-mg 8213A-58, CM 226070	40	71	88	NA
500-mg 8213A-59 CM 228070	45	77	93	NA
1000-mg 8213A-61 CM 233070	37	74	85	NA
PROCANBID				
500-mg 8213A-60 CM 230070 N=70,000	7	32	55	71
1000-mg 8213A-46A1 CM 342119 N=100000	9	39	61	75

Study Subjects: 43 subjects were enrolled, 6 women and 37 men aged 31 to 78 years. With regard to race, all were white except 2 that were black and 3 classified as "others". Subjects were characterized with regard to height, weight, and serum creatinine.

Effect Measurements: Reported in Study 6.

Blood Sampling: Four different portions of the plasma concentration time curve were characterized:

a) The first 24 hours of active treatment (17 samples, Period 1);

b) the 5th day (13 samples) of continuous treatment in Period 1;

c) the 6th day (13 samples) of continuous treatment in Period 2 (after administration of the last dose or doses);

d) the 36 hours following the last dosing interval (9 samples).

In addition, two "trough" plasma samples (at times -12 hours and -24 hours) were taken during each day preceding an extensively characterized day to establish steady-state.

Urine Sampling: 6-hour fractions of urine (a total of 10) were collected during time periods when plasma levels were characterized.

Pharmacokinetic Evaluation: In addition to using the Cp data as such, and recording T_{max} and C_{max}, the average steady-state level C_{avg} was calculated as the AUC of the dosing interval divided by the interval length. A fluctuation index was calculated as $(C_{max} - C_{min})/C_{avg}$. Also, CL_{rcn} was calculated for parent drug and NAPA.

Statistical Methods: The main parameters for comparing the two formulations were the dose-normalized C_{min}, C_{max}, and C_{avg} (in the following denoted with the prefix n, e.g. nC_{max}). These data were log-transformed and analyzed by ANOVA. Both the dose-proportionality evaluation and the comparison between the two formulations were done this way. Judgment whether dose-proportionality was present or formulations were bioequivalent were based on 90% confidence intervals of the least-squares mean ratios.

STUDY RESULTS:

Plasma concentration profiles: The mean plasma concentration profiles at steady-state (based on data from visits 5 and 7) are presented in Figure 1 for procainamide and Figure 2 for NAPA.

Dose proportionality: The C_{max} values for the three strengths of Procan SR and PROCANBID are shown in Figure 3. Plots of C_{min} and C_{avg} gave similar plots, demonstrating that concentrations tended to increase more than in proportion to dose for both formulations. The 90% confidence intervals for log-transformed nC_{max} values, indicated substantial deviations from dose proportionality for PROCANBID, and findings for Procan SR were similar. In contrast, the data for NAPA were nearly dose proportional for the two formulations.

The deviation from linearity did not seem to be explained by differences in *in vitro* dissolution rates, as the 500-mg Procan SR tablet was faster dissolving than the 1000-mg Procan SR tablet. Furthermore, the same formulation was used to obtain the 2000-mg/day and the 4000-mg/day doses of PROCANBID.

Comparison between PROCANBID and Procan SR: Individual and mean values for nC_{max} for PROCANBID and Procan SR were similar. Statistical testing at all three dose levels showed that 90% confidence intervals of least squares mean nC_{max} values were within the 80-125% range normally used for bioequivalence testing. The same held true for nC_{avg} which is a measure of extent of bioavailability. For nC_{min}, however, lower values were found after PROCANBID, and confidence intervals extended below the 80-125% range. Table 1 below is a further condensed summary of the data, in which data from all dose groups have been analyzed together.

Table 1. Mean pharmacokinetic parameters for procainamide, during steady-state following multiple doses of PROCANBID and Procan SR; all dose levels combined.

Parameter	PROCANBID (test)	Procan SR (ref.)	Test/Ref	90% Confidence interval*
nC_{max} (mg/L)	2.78	2.80	0.99	92-104
T_{max} (hr)	4.3	3.7	1.15	-
nC_{avg} (mg/L)	2.02	2.2	0.92	86-98
nC_{min} (mg/L)	1.39	1.68	0.83	74-89
$(C_{max} - C_{min})/C_{avg}$	0.712	0.549	1.3	115-144

*) Based on log-transformed data except for fluctuation index.

Discussion: The lack of dose proportionality in the present study is difficult to interpret, since the design was not cross-over with respect to the three dose levels, and there was large interindividual variability in critical factors such as age and creatinine clearance. The fact that the lack was observed with both the new and old formulation indicates that it is not formulation related. It also appeared unrelated to variability in the *in vitro* release rates of the products.

Conclusions: In view of the suboptimal design for studying dose proportionality, the present study, although indicative of possible nonlinearity in the disposition of procainamide, should be regarded as inconclusive.

The comparison between PROCANBID and Procan SR indicates that the performance of two drugs was bioequivalent in the present dosage regimens in terms of C_{max} and C_{avg} but not in terms C_{min}. The lower C_{min} with PROCANBID results in larger fluctuation within the dosage interval with this product.

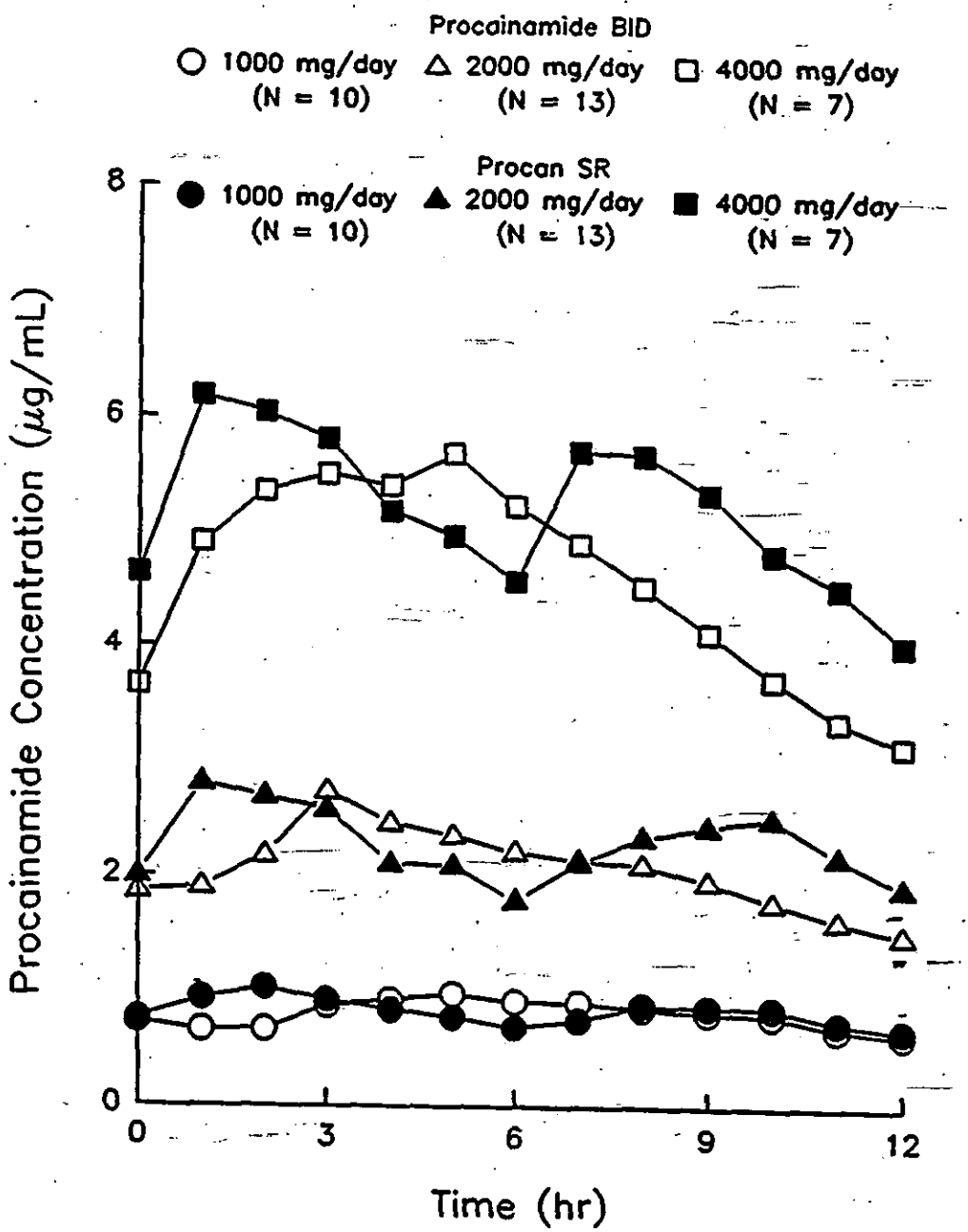


Figure 1. Mean plasma procainamide concentrations at steady-state following administration of PROCANBID tablets q12h (open symbols) or Procan SR tablets q6h (filled symbols). Data from visits 5 and 7 were pooled.

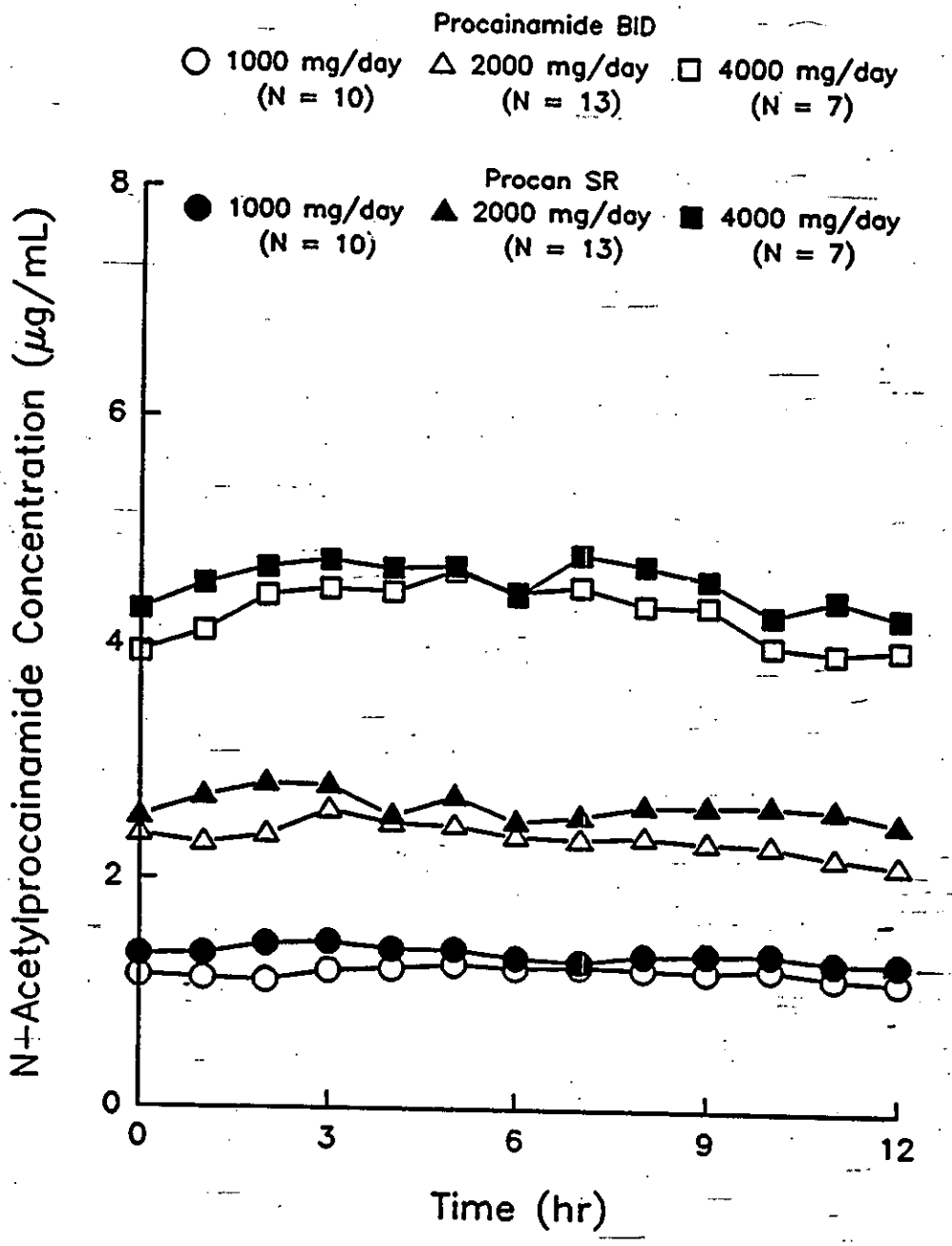


Figure 2. Mean plasma NAPA concentrations at steady-state following administration of PROCANBID tablets q12h (open symbols) or Procan SR tablets q6h (filled symbols). Data from visits 5 and 7 were pooled.

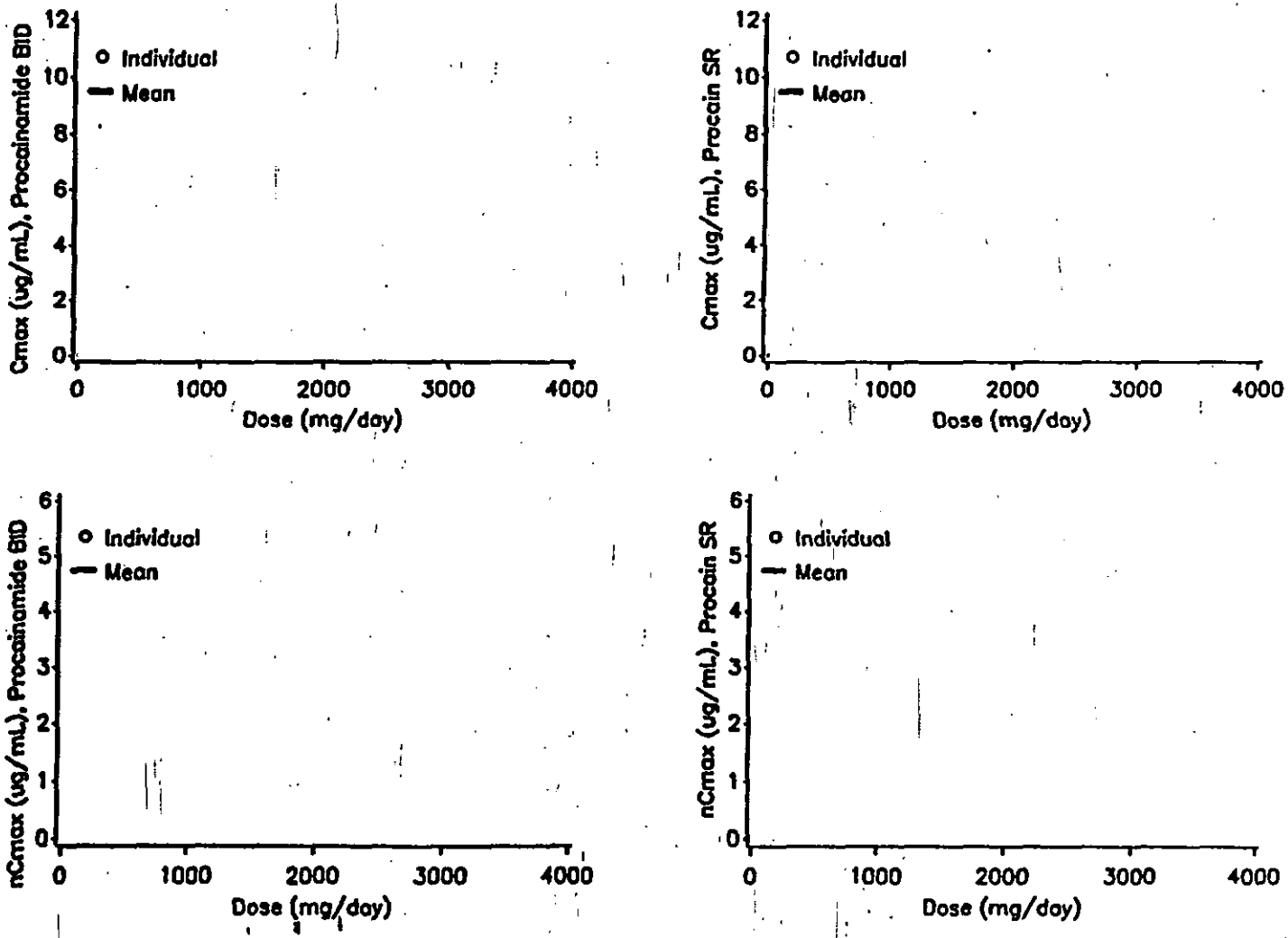


Figure 3. Individual and mean procainamide C_{max} and nC_{max} values following administration of PROCANBID tablets q12h (left) and Procan SR tablets q6h (right). The dotted lines were drawn through the origin and the highest mean value.

Study 6: Evaluation of the relationship between plasma levels and pharmacologic effect.

Study Title: A double-blind, parallel-group, formulation-crossover, placebo-controlled, multicenter study comparing the activity of a new formulation of procainamide administered bid to suppress ventricular premature depolarizations.

Study Number: Protocol 610-43, reported in RR 764-02212 (this report), RR-720-03128 (clinical report), RR-764-02031 (pharmacokinetic report).

Volume Number and Pages: 1.14

Objectives: 1) To demonstrate the pharmacological equivalence of market formulation Procan SR administered QID and a new formulation of procainamide administered BID (addressed in 720-03128; see Medical Review)

2) to characterize by pharmacokinetic/pharmacodynamic (PK/PD) methods the relationship between plasma concentration and pharmacologic effect (addressed in RR-764-02212; this report);

3) to evaluate procainamide and NAPA (N-acetylprocainamide) pharmacokinetics as a function of dose and treatment (addressed in RR-764-02031; Study 5).

Design: A 1-week wash-out followed by a 2-week double-blind formulation-crossover treatment. Patients were randomized to 1 of 4 dose levels (see table below) and to either the Procan SR (QID) formulation or the procainamide BID formulation in the first week. Maintaining the dose, they were then crossed over to the alternative formulation in the second week without a washout between treatments.

Dose Level (mg/day)	Sequence	Period 1	Period 2
0 (placebo)	A	QID	BID
	B	BID	QID
1000	C	QID	BID
	D	BID	QID
2000	E	QID	BID
	F	BID	QID
4000	G	QID	BID
	H	BID	QID

Treatments: Study medications were Procan SR: 250-mg, 500-mg, 1000-mg, and placebo tablets, and procainamide BID: 500-mg, 1000-mg, and placebo tablets all manufactured in [ ]. [ ] (In the submission it was stated that site of manufacture was [ ] When questioned about this, the firm states that this was an error).

Study Subjects: 43 subjects were enrolled, 6 women and 37 men aged 31 to 78 years. With regard to race, all were white except 2 that were black and 3 classified as "others". Subjects were characterized with regard to height, weight, and serum creatinine.

Effect Measurements: Holter monitoring was performed for 48 hours
a) during the Baseline Period,
b) during the last 2 days of treatment in Period 1, and
c) during the last 2 days of treatment in Period 2.

In addition, 24-hour Holter monitoring was performed
d) after initiation of active drug treatment (Period 1) and
e) following the last dosing interval.

Ventricular Premature Depolarizations (VPD) were evaluated as number of events/0.5 hour, as the average (VPDavg) over 12 hours, and as the maximal rate over 12 hours (VPDmax).

Blood Sampling: Four different portions of the plasma concentration time curve were characterized:

a) The first 24 hours of active treatment (17 samples, Period 1);

b) the fifth day (13 samples) of continuous treatment, Period 1;

c) the 6th day (13 samples) of continuous treatment in Period 2 (after administration of the last dose or doses);

d) the 36 hours following the last dosing interval (9 samples).

In addition, two "trough" plasma samples (at times -12 hours and -24 hours) were taken during each day preceding an extensively characterized day to establish steady-state.

Assay: [ ]

Pharmacokinetic Evaluation: This is reviewed in Study 5.

PK-PD analysis using Mixed Effects Modeling: NONMEM, Version IV, Level 2.0 on an IBM 3090 Model 200E system operating under MVS/ESA 4.1 with a FORTRAN COMPILER version 2 was used to evaluate the relationship between plasma levels and effect (number of VPDs). The pharmacologic effect that was modeled was the rate of VPD. A true PK-PD modeling was not undertaken since a

pharmacokinetic model was not used to describe PA plasma level, and time was not a variable. Instead the relationship between plasma levels of procainamide (PA) and N-acetylprocainamide (NAPA) and effect was evaluated during what was considered steady-state intervals [see above under Effect Measurements a), b), and c)]. Thus all 24-hour data from the first dosing interval were excluded from analysis. All data from visit 7, i.e., the 24 hours following the last dosing interval in Period 2 when drug treatment had been discontinued were modeled separately.

RESULTS: A summary of the demographic data of the 4 study groups is presented in Table 1. Examples of VPD changes and concentration profiles in representative individuals are presented in Figures 1, 2, and 3.

There was a large intraindividual variability in change in VPD. There was no consistent pattern of change in VPD in relation to time or to concentration data, nor was there any evidence for concentration-effect hysteresis. Taken together, this data indicated that traditional PK-modeling was not warranted. Instead the objective was defined as finding the relationship between plasma data at steady-state and effect. VPD rates at steady-state were plotted against demographic parameters, and age was identified as a possible covariate. The dose-group mean VPD rates at steady-state are plotted against C_{pa} and dose in Figure 4.

Initial models: Initial modeling attempts were based on individual average of change in VPD and C_{avg} during steady-state. The step-wise procedure to develop the model is presented in Table 2. A simple inhibitory E_{max} model was found to be a reasonable representation of the data.

Main model: The primary evaluation was based on hourly VPD and C_{pa} data. The development of the model is presented in Table 3. As with the average data, an inhibitory E_{max} model was the "preferred" model describing the relationship between VPD rate and Cpa, with age influencing both the maximal attainable suppression (E_{max}) and I_{50}:

$$VPD = 1.25 * AGE * FORM * [1 - C_{pa}/(-3.92 + 0.130*AGE + C_{pa})]$$

Here FORM stands for θ_3 = 1.99 for QID, θ_4 =2.03 for BID, and 1.00 for placebo formulations. A proportional error was assumed for E_{max}. I_{50} was assumed to be constant.

A proportional error was assumed for VPD. The results indicated that interindividual variability (%SD) for E_{max} was 104%. The intraindividual variability for VPD was 93%.

The model indicates a very strong effect of age on the I_{50} (at 31 years I_{50} was 0.11 mg/L; at 78 years it was 6.2 mg/L). Drug

response thus appears to decline with age. The authors state that although I_{50} is in gross agreement with "therapeutic ranges" observed for PA (4 to 10 μg/mL), it is very vaguely defined by the model due to large standard errors. Population mean predicted values based on this model and the analogous model arrived at for NAPA (model B17) at an average age of 62.8 years are presented in Figure 5.

Without the FORM parameter, the Cp-PD model does not progress continuously from low plasma levels to zero plasma levels (placebo). As can be seen from Figure 5, the lower range of PA and NAPA concentrations include a number of instances of VPDs higher than baseline. This is even more evident when the mean levels are examined (See Figure 4).

Other models: During the development of models based on average VPD and C_{avg} data, attempts using C_{min} rather than C_{avg} data had only slight effects on parameter values and statistics. Also models based on data from visit 7 (declining phase) were in gross agreement with the "preferred" model. When modeling hourly VPD rates and concentration, attempts to include concentration data for both PA and NAPA (=met) by inclusion of ($C_{met} + \theta * C_{pa}$) resulted in a θ value close to 0. A model including only C_{met} (model B17) was essentially identical to the "preferred" model. It was concluded that NAPA levels provided the same information as the PA levels, and that no substantial improvement could be obtained with simultaneous inclusion of the two.

Discussion: It appears from the overall mean data that there is an increased rate of VPD at the lowest dose (1000 mg/day) and hence at low plasma concentrations. This prevents the modeling of VPD as a continuous and monotonous decline with increasing concentration of either PA or NAPA. It is important to note, therefore, that the outcome of the entire study of 77 patients is different (see RR-720-03128 and the Medical Officer's review), in that the 1000 mg/day dose showed an average (all patients, BID and QID dosage) VPD decrease of 17.7% from the baseline. The decrease in VPD for the other doses do not differ between the main study and the present study, which is based on a subset of 43 subjects. The explanation for the different outcome in the sub-study is probably a large intra-subject variability in VPD and a weak and variable drug response. As an illustration of the latter, there was neither any significant difference in response between any of the three doses of the QID formulation and placebo, nor was there a difference when these dose groups were combined.

Since the FORM values found for BID and QID dosage were virtually identical, the model indicates that PA acts identically whether it is released from the old or the new formulation. However, this fact does not support the firm's claim (see Conclusions p.14 of

the Report) that 'Administration of procainamide BID tablets every 12 hours is equivalent to administration of procainamide QID tablets every 6 hours with respect to VPD suppression'. This is so because the model does not include the temporal aspects of drug treatment, and the plasma concentration-time profiles are far from identical for the two formulations.

The authors state that there was no indication of hysteresis in the data. Their conclusion was that there was no reason to develop a true PK-PD model. While it appears to be perfectly reasonable to disregard the time dependency in the data, the same reasoning could have been used to justify inclusion of the study phases where drug levels were rising or falling.

Conclusions: No definite conclusions can be drawn from the evaluation of the concentration-effect relationship. The reasons for this appear to be:

1) A large intra- and inter-subject variability of the effect at a particular concentration and

2) A weak response to the drug.

Tentatively, a decreased effect of drug treatment with increasing age was identified.

11. FIGURES

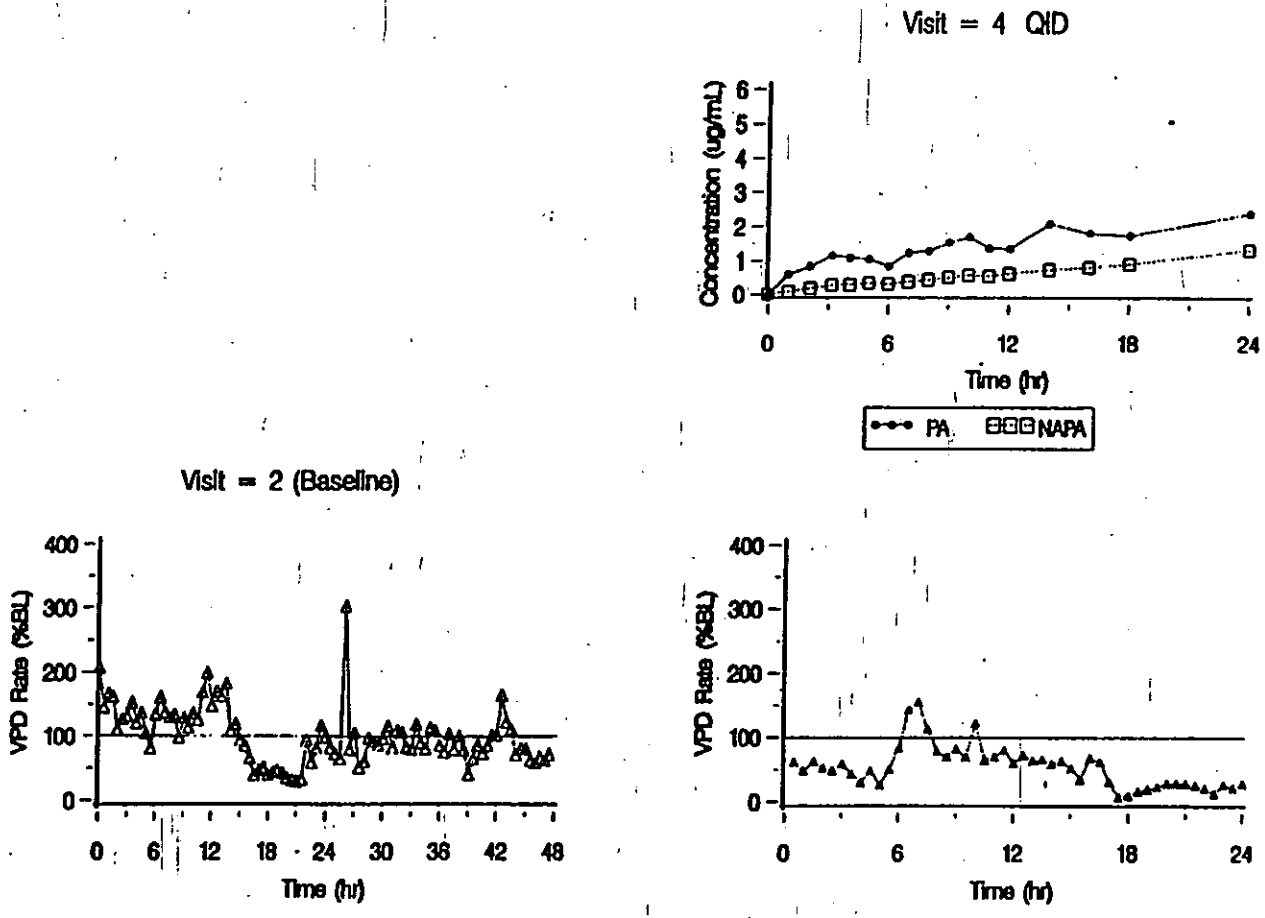


Figure 1. Plasma PA and NAPA Concentration Data and Holtor Monitor Record (0.5-hr Segments) for a Representative Patient (202, 2000 mg/day) Prior to Treatment (Baseline; Visit 2) and Following the Initial Procainamide QID or BID Dose (Visit 4). VPD rates are expressed as percentage of average rate (% baseline) during 48-hour interval at Visit 2 (Protocol 610-43).

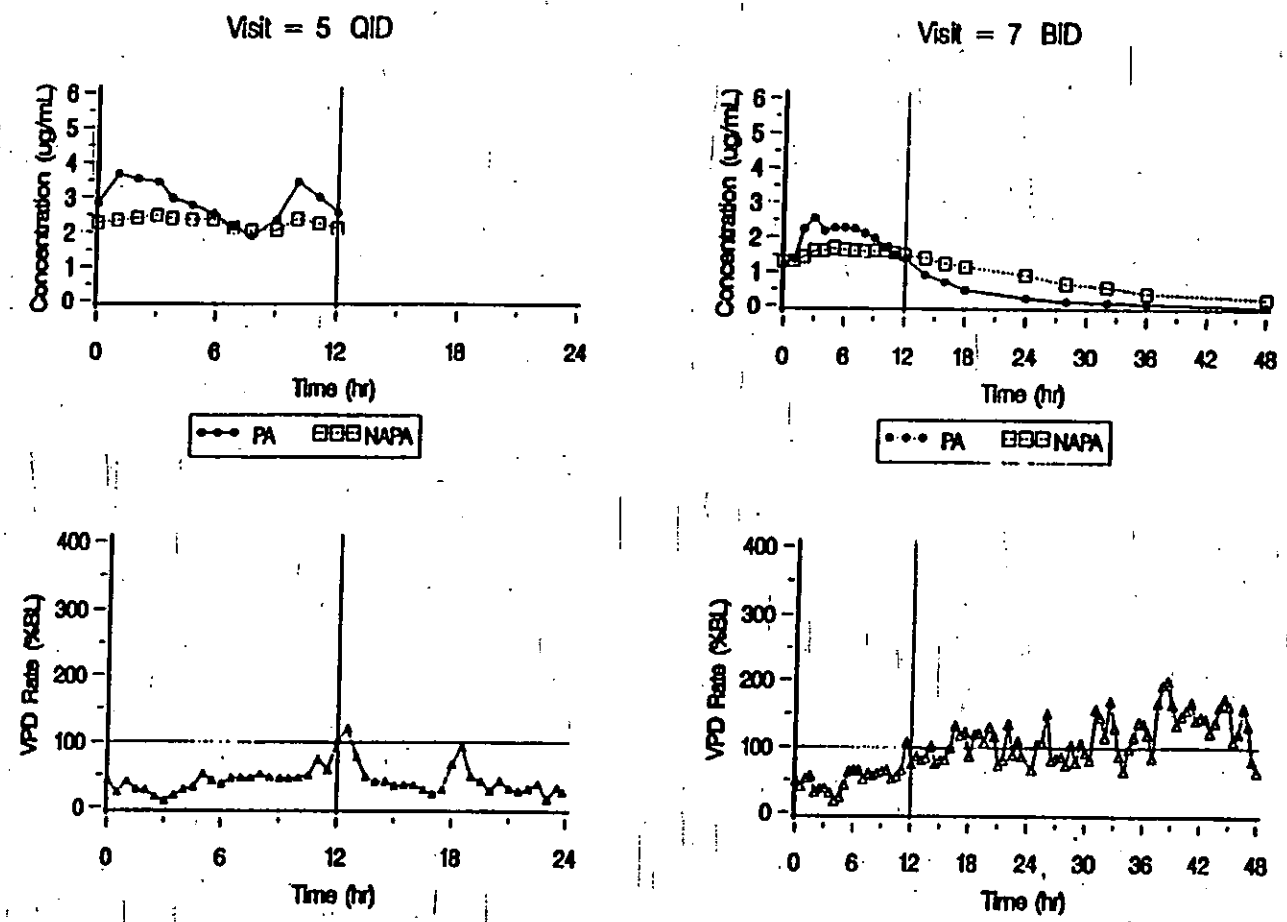


Figure 2. Plasma PA and NAPA Concentration Data and Holtor Monitoring Record (0.5 hr Segments) for a Representative Patient (202, 2000 mg/day) During the First (Visit 5) and Second (Visit 7) 12-Hour Steady-State Intervals and Following the Final Dose During Visit 7. VPD rates are expressed as percentage of average rate (% baseline) during 48-hour interval at Visit 2 (Protocol 610-43).

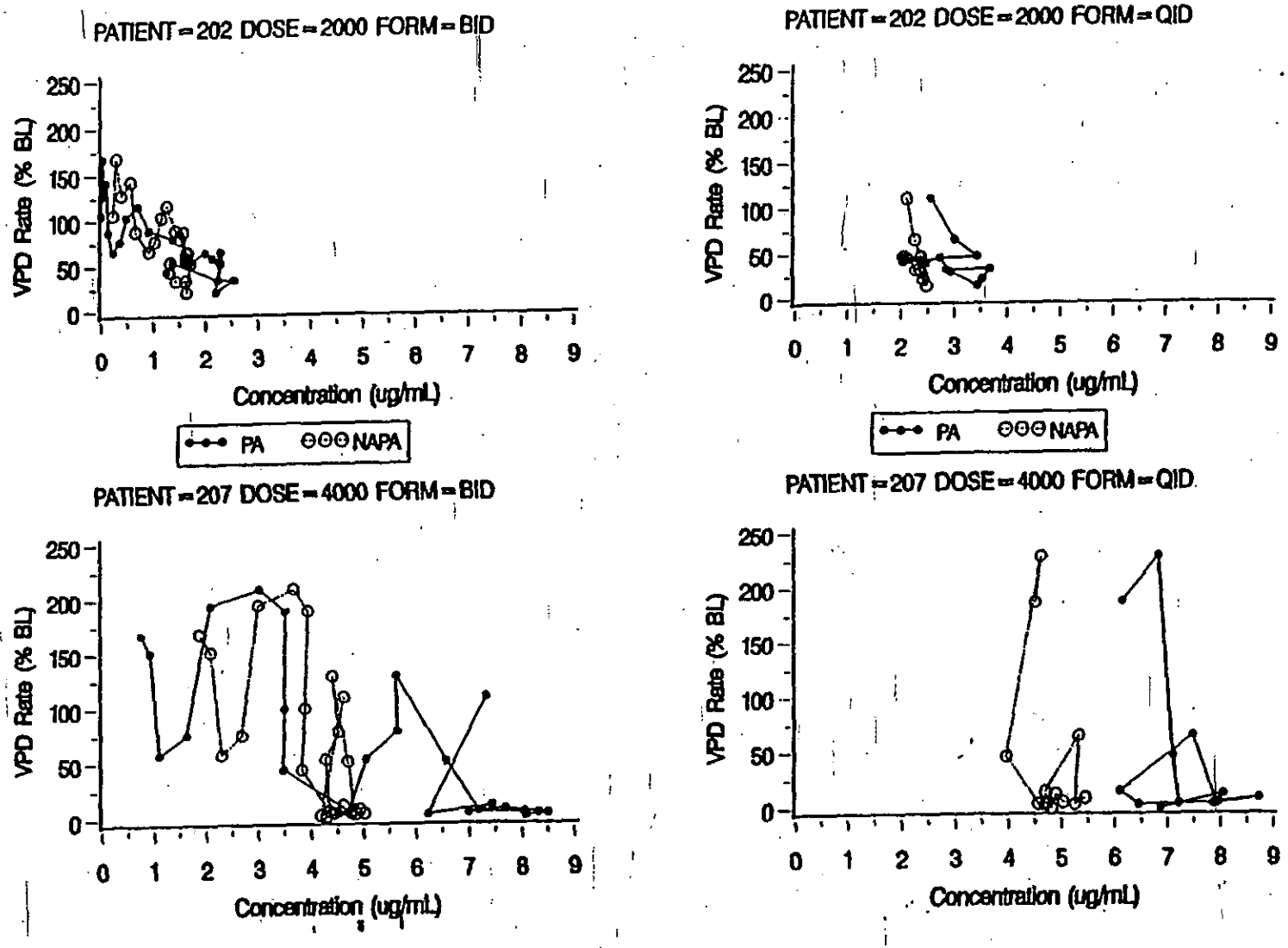
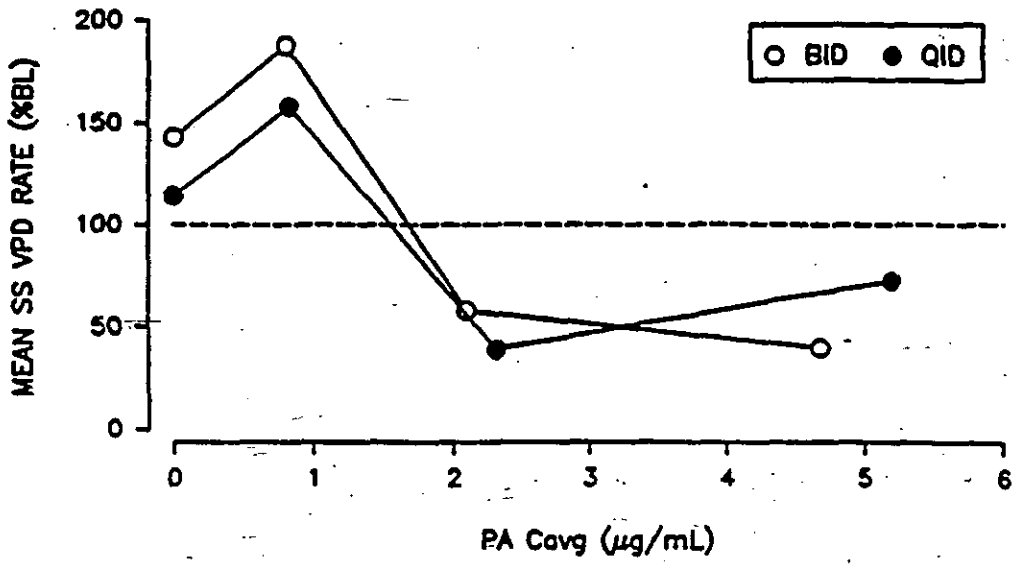


Figure 3. Hourly VPD Rate Values Versus Plasma PA and NAPA Concentration Plots For 2 Representative Patients (Protocol 610-43)



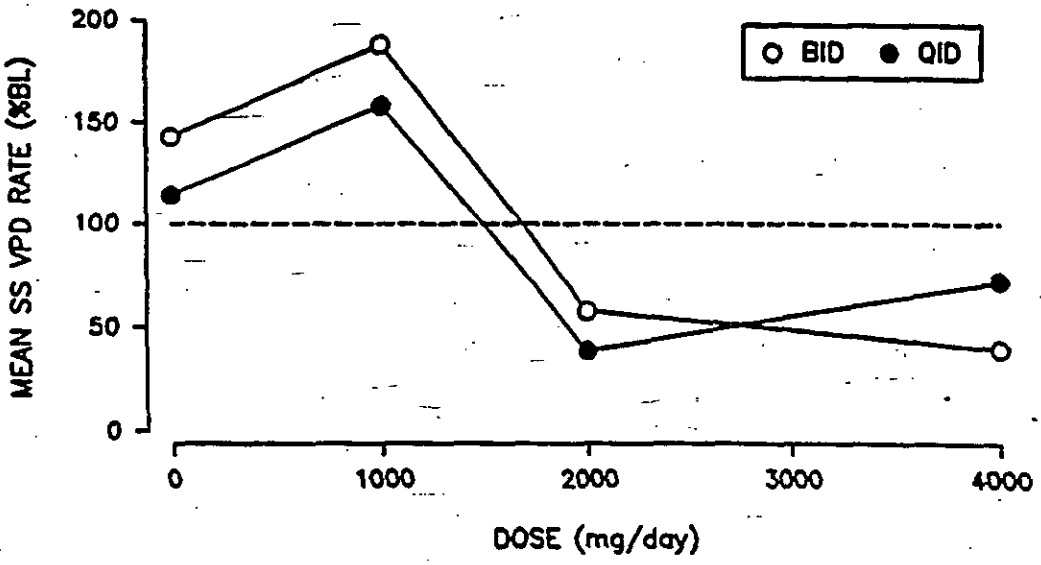


Figure 4. Dose-group mean steady-state VPD Rate (VPDavg) *versus* either mean procainamide concentration (Cavg) or dose. Placebo values assigned as "BID" or "QID" as specified in study protocol.

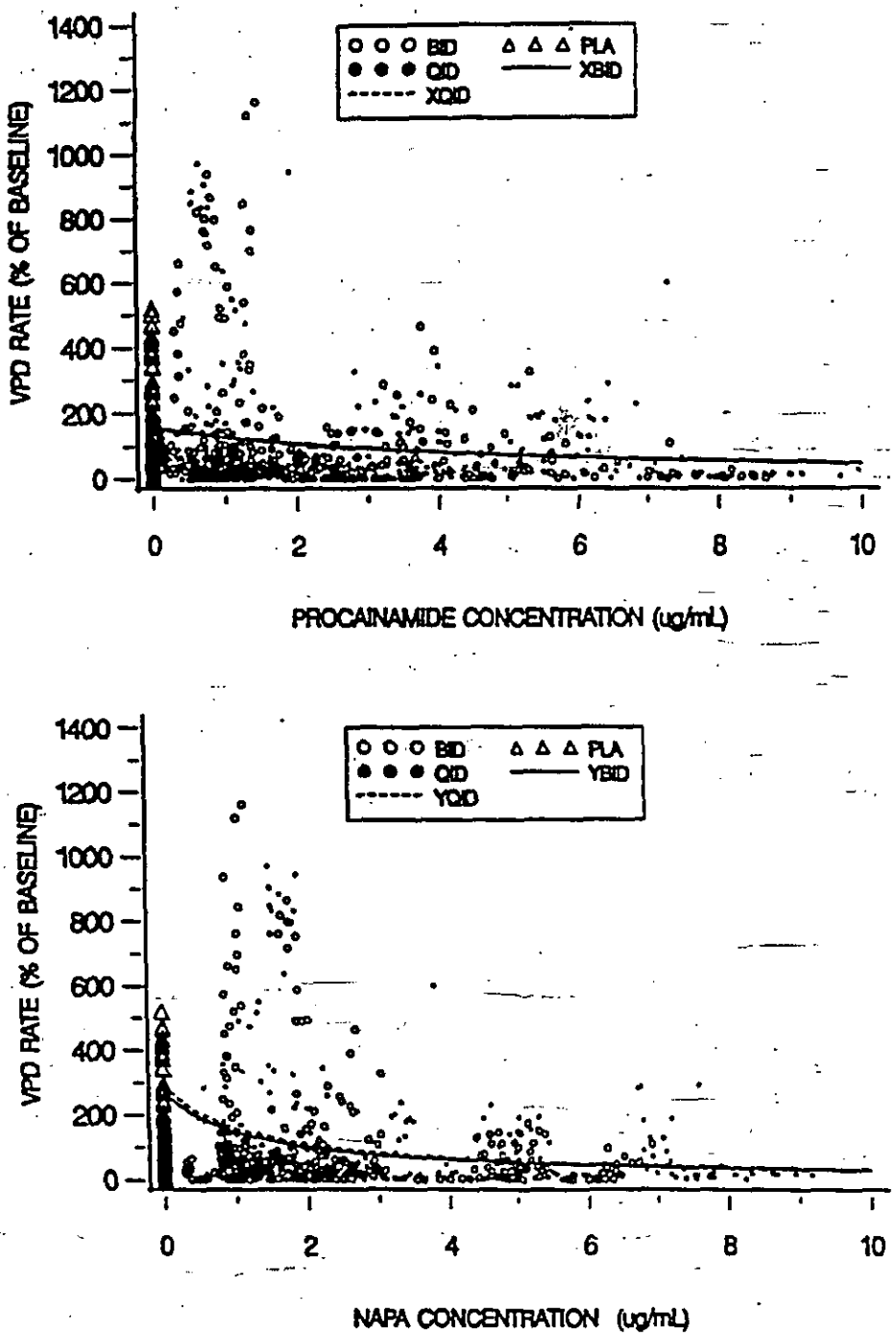


Figure 5. Hourly VPD Rate Versus Observed PA (Upper Panel) and NAPA (Lower Panel) Concentrations for Placebo (PLA), and BID and QID Tablets During 12-Hour Steady-State Intervals. Population mean predicted values for procainamide BID (XBID) and QID tablets (XQID) based on PA model [B13] at an average (N = 42) patient age of 62.8 years are indicated in the upper panel. Corresponding predicted values (YBID and YQID) based on NAPA model [B17] are indicated in the lower panel (Protocol 610-43).

TABLE 1. Demographic Data for Patients Enrolled in Protocol 610-43

Patient[a]	Weight (kg)	Height (cm)	Age (yr)	Race	Sex	Creatinine Clearance (mL/min)	Body Surface Area (m^2)
			Dose = Placebo				
101	88.9	182	31	W	M	89.7	2.10
201	95.2	168	66	W	M	75.3	2.04
205	72.8	175	66	B	M	41.6	1.88
301	78.0	188	67	W	M	79.1	2.04
305	102.0	188	67	W	M	69.0	2.28
410	75.7	168	66	W	M	59.9	1.85
413	78.5	180	56	W	M	76.3	1.98
502	95.2	168	64	O	M	77.3	2.04
504	94.8	178	73	W	M	58.8	2.13
509	84.8	168	43	W	M	81.6	1.94
515	106.6	180	70	W	M	86.3	2.26
			Dose = 1000 mg/day				
203	98.4	165	73	W	M	53.9	2.05
302	92.5	175	65	W	M	64.3	2.08
306	85.7	180	66	W	M	48.9	2.06
411	116.1	183	60	W	M	86.0	2.37
503	88.0	178	78	W	M	58.3	2.06
505	81.6	165	71	O	F	73.6	1.89
510	91.2	180	64	W	M	80.2	2.11
512	68.0	173	51	B	M	64.7	1.81
601	83.5	185	73	W	M	55.5	2.08
602	99.8	183	68	W	M	62.4	2.22
			Dose = 2000 mg/day				
202	71.2	165	72	W	M	42.0	1.78
206	90.0	179	72	W	M	56.7	2.09
303	72.6	175	78	W	M	41.7	1.88
307	92.1	193	38	W	M	108.7	2.23
309	47.6	168	62	W	F	29.1	1.52
409	84.8	170	68	W	M	56.5	1.97
414	59.9	160	44	W	F	48.3	1.62
501	100.7	178	61	W	M	100.4	2.18
507	55.3	152	67	W	F	39.6	1.51
511	75.7	166	38	W	M	82.5	1.84
516	83.9	157	47	W	F	102.0	1.85
517	103.4	191	70	W	M	67.0	2.32
603	89.8	180	61	W	M	65.7	2.10
			Dose = 4000 mg/day				
204	77.8	188	68	W	M	55.6	2.04
207	69.6	165	58	W	M	49.5	1.77
304	95.7	180	74	W	M	67.5	2.16
308	82.5	177	67	W	M	55.8	1.99
412	104.3	168	67	W	F	52.7	2.12
506	65.3	178	70	W	M	39.7	1.82
508	68.9	178	56	W	M	61.9	1.86
513	93.0	178	64	W	M	81.8	2.11
514	71.7	178	65	O	M	62.2	1.89

W = White; B = Black; O = Other.

[a] The first digit indicates center, the second and third patient number at center.

Table 2. Population Concentration-Effect Modeling of Average VPD Rate (VPDavg) As a Function of Average (Cavg) and Minimum (Cmin) Procainamide Concentrations and Average NAPA (Cavm) Concentration During 12-Hour Steady-State Intervals (74 observations for 42 patients) (Protocol 610-43)
(Page 1 of 5)

Test/Hypothesis	Model	θ (SE)	ω^2,σ^2 (SE)	Fitting Stats	Conclusions
Linear Models Based on Procainamide Cavg, Cmin and Dose					
VPD rate is described by overall mean value $\eta_1 \sim N(0,\omega_{11})$ $\epsilon \sim N(0,\sigma_{11})$	[A1] Run 6210830 VPD = $\theta_1 * (1 + \eta_1)$ Y = VPD * $(1 + \epsilon_1)$	θ_1 = 96.5 (17.9)	ω_{11} = 1.21 (0.32) σ_{11} = 0.403 (0.174)	759.209 MRST 3.2 SigDig	base model
VPD rate is linear function of age	[A2] Run 10061002 INT = θ_1 COA = $\theta_2 * (1 + \eta_1)$ VPD = INT + COA * AGE Y = VPD * $(1 + \epsilon_1)$	θ_1 = -36.0 (38.5) θ_2 = 2.10 (0.781)	ω_{11} = 0.559 (0.343) σ_{11} = 0.340 (0.118)	744.142 MRST 3.1 SigDig	[A1] - [A2] = 15.1 age is covariate
VPD rate is linear function of Cavg	[A3] Run 6210831 INT = $\theta_1 * (1 + \eta_1)$ SLP = θ_2 VPD = INT + SLP * CAVG Y = VPD * $(1 + \epsilon_1)$	θ_1 = 112 (23.9) θ_2 = -9.28 (6.87)	ω_{11} = 0.786 (0.299) σ_{11} = 0.439 (0.210)	755.545 MRST 3.5 SigDig	[A1] - [A3] = 3.7 simple linear model
Formulation affects linear concentration model; TABQ = 1 if QID, 0 otherwise TABB = 1 if BID, 0 otherwise	[A4] Run 10061003 INT = $\theta_1 * (1 + \eta_1)$ SLP = θ_2 VPD1 = INT + SLP * CAVG VPD2 = VPD1 * $\theta_3^{TABQ} * \theta_4^{TABB}$ Y = VPD2 * $(1 + \epsilon_1)$	θ_1 = 93.9 (23.7) θ_2 = -3.38 (5.26) θ_3 = 0.989 (0.368) θ_4 = 1.36 (0.517)	ω_{11} = 0.978 (0.318) σ_{11} = 0.285 (0.0833)	744.737 MRST 3.2 SigDig	[A3] - [A4] = 10.8 formulation index is important
Age affects slope of linear model	[A5] Run 10061004 INT = $\theta_1 * (1 + \eta_1)$ SLP = $\theta_2 + \theta_5 *$ AGE VPD1 = INT + SLP * CAVG VPD2 = VPD1 * $\theta_3^{TABQ} * \theta_4^{TABB}$ Y = VPD2 * $(1 + \epsilon_1)$	θ_1 = 96.9 (24.4) θ_2 = -81.5 (25.5) θ_3 = 0.939 (0.336) θ_4 = 1.30 (0.445) θ_5 = 1.23 (0.412)	ω_{11} = 0.906 (0.250) σ_{11} = 0.258 (0.0845)	734.586 MRST 3.2 SigDig	[A4] - [A5] = 10.2 age is covariate

Table 2. Population Concentration-Effect Modeling of Average VPD Rate (VPDavg) As a Function of Average (Cavg) and Minimum (Cmin) Procainamide Concentrations and Average NAPA (Cavm) Concentration During 12-Hour Steady-State Intervals (74 observations for 42 patients) (Protocol 610-43)
(Page 2 of 5)

Test/Hypothesis	Model	θ (SE)	ω^2,σ^2 (SE)	Fitting Stats	Conclusions
Concentration and age effects are additive; $\eta_2 \sim N(0,\omega_{22})$	[A6] Run 10061005 INT = θ_1 SLP = $\theta_2 * (1 + \eta_1)$ COA = $\theta_3 * (1 + \eta_2)$ VPD = INT + SLP * CAVG + COA * AGE Y = VPD * $(1 + \epsilon_1)$	θ_1 = -29.5 (42.1) θ_2 = -11.5 (2.24) θ_3 = 2.14 (0.872)	ω_{11} = 9.57 (6.86) ω_{12} = 2.88 (2.05) ω_{22} = 0.950 (0.740) σ_{11} = 0.401 (0.132)	728.318 MRST 3.9 SigDig	[A5] - [A6] = 6.3 superior to preceding but variances large
Formulation affects additive model	[A7] Run 10061006 (APDX) INT = θ_1 SLP = $\theta_2 * (1 + \eta_1)$ COA = $\theta_5 * (1 + \eta_2)$ VPD1 = INT + SLP * CAVG + COA * AGE VPD2 = VPD1 * $\theta_3^{TABQ} * \theta_4^{TABB}$ Y = VPD2 * $(1 + \epsilon_1)$	θ_1 = -35.6 (33.4) θ_2 = -7.50 (2.52) θ_3 = 0.935 (0.317) θ_4 = 1.32 (0.439) θ_5 = 1.96 (0.814)	ω_{11} = 21.3 (12.1) ω_{12} = 4.59 (2.35) ω_{22} = 1.06 (0.657) σ_{11} = 0.304 (0.0871)	717.276 MRST 3.9 SigDig	[A5] - [A7] = 17.3 [A6] - [A7] = 11.0 formulation index important; variances large
Substitute Cmin for Cavg in [A7]	[A8] Run 10061007 INT = θ_1 SLP = $\theta_2 * (1 + \eta_1)$ COA = $\theta_5 * (1 + \eta_2)$ VPD1 = INT + SLP * CMIN + COA * AGE VPD2 = VPD1 * $\theta_3^{TABQ} * \theta_4^{TABB}$ Y = VPD2 * $(1 + \epsilon_1)$	θ_1 = -53.5 (27.1) θ_2 = -9.38 (3.43) θ_3 = 0.860 (0.292) θ_4 = 1.20 (0.403) θ_5 = 2.34 (0.832)	ω_{11} = 23.7 (13.7) ω_{12} = 4.16 (1.67) ω_{22} = 0.797 (0.313) σ_{11} = 0.304 (0.0755)	717.360 MRST 3.1 SigDig	[A7] - [A8] = -0.1 Cmin and Cavg convey same information
Substitute dose for Cavg in [A7]	[A9] Run 10061010 INT = θ_1 SLP = $\theta_2 * (1 + \eta_1)$ COA = $\theta_5 * (1 + \eta_2)$ VPD1 = INT + SLP * DOSE + COA * AGE VPD2 = VPD1 * $\theta_3^{TABQ} * \theta_4^{TABB}$ Y = VPD2 * $(1 + \epsilon_1)$	θ_1 = -20.2 (25.9) θ_2 = -0.00697 (0.0064) θ_3 = 1.07 (0.404) θ_4 = 1.41 (0.505) θ_5 = 1.58 (0.632)	ω_{11} = 27.6 (59.3) ω_{12} = 6.54 (8.39) ω_{22} = 1.60 (1.13) σ_{11} = 0.398 (0.123)	717.511 MRST 3.2 SigDig	[A7] - [A9] = -0.2 [A8] - [A9] = -0.2 Cavg and Cmin convey same information as does dose

Table 2. Population Concentration-Effect Modeling of Average VPD Rate (VPDavg) As a Function of Average (Cavg) and Minimum (Cmin) Procainamide Concentrations and Average NAPA (Cavm) Concentration During 12-Hour Steady-State Intervals (74 observations for 42 patients) (Protocol 610-43)

(Page 3 of 5)

Test/Hypothesis	Model	θ (SE)	ω^2,σ^2 (SE)	Fitting Stats	Conclusions
Emax Models Based on Procainamide Cavg, Cmin and Dose					
VPD rate is related to Cavg by inhibitory Emax model; Emax constrained to equal baseline.	[A10] Run 6210900 EMAX = θ_1 * (1 + η_1) I50 = θ_2 VPD1 = EMAX - EMAX * CAVG / (I50 + CAVG) Y = VPD1 * (1 + ϵ_1)	θ_1 = 117 (27.6) θ_2 = 6.01 (4.10)	ω_{11} = 1.03 (0.276) σ_{11} = 0.463 (0.179)	752.232 MRST 3.8 SigDig	[A2] - [A10] = -8.1 simple Emax model
Submaximal Emax model	[A11] Run 6210902 EMAX = θ_1 * (1 + η_1) I50 = θ_2 BASE = θ_3 VPD1 = BASE - EMAX * CAVG / (I50 + CAVG) Y = VPD1 * (1 + ϵ_1)	θ_1 = 28.2 (73.0) θ_2 = -0.14 (0.447) θ_3 = 120 (49.9)	ω_{11} = 11.9 (52.5) σ_{11} = 0.602 (0.165)	763.669 MRST 3.2 SigDig	[A10] - [A11] = -11.4 complexity not justified; maximal VPD suppression occurs
Formulation affects inhibitory Emax model	[A12] Run 6211400 EMAX = θ_1 * (1 + η_1) I50 = θ_2 VPD1 = EMAX - EMAX * CAVG / (I50 + CAVG) VPD2 = VPD1 * θ_3^{TABQ} * θ_4^{TABB} Y = VPD2 * (1 + ϵ_1)	θ_1 = 91.5 (22.9) θ_2 = 5.48 (6.12) θ_3 = 1.29 (0.630) θ_4 = 1.68 (0.808)	ω_{11} = 0.958 (0.216) σ_{11} = 0.345 (0.0950)	740.562 MRST 4.3 SigDig	[A10] - [A12] = 11.7 formulation index important; VPD rate high at low conc;
Age affects Emax and I50	[A13] Run 7091300 (APDX) EMAX = θ_1 * AGE * (1 + η_1) I50 = θ_2 + θ_5 * AGE VPD1 = EMAX - EMAX * CAVG / (I50 + CAVG) VPD2 = VPD1 * θ_3^{TABQ} * θ_4^{TABB} Y = VPD2 * (1 + ϵ_1)	θ_1 = 1.67 (0.438) θ_2 = -4.02 (4.75) θ_3 = 1.08 (0.496) θ_4 = 1.41 (0.633) θ_5 = 0.137 (0.143)	ω_{11} = 0.801 (0.189) σ_{11} = 0.346 (0.0945)	724.983 MRST 3.7 SigDig	[A7] - [A13] = -7.7 [A12] - [A13] = 15.6 age and formulation index are both important; best Emax model

Table 2. Population Concentration-Effect Modeling of Average VPD Rate (VPDavg) As a Function of Average (Cavg) and Minimum (Cmin) Procainamide Concentrations and Average NAPA (Cavm) Concentration During 12-Hour Steady-State Intervals (74 observations for 42 patients) (Protocol 610-43)

(Page 4 of 5)

Test/Hypothesis	Model	θ (SE)	ω^2,σ^2 (SE)	Fitting Stats	Conclusions
Substitute Cmin for Cavg in [A13]	[A14] Run 7111600 (APDX) EMAX= θ_1 * AGE * (1 +η_1) I50 = θ_2 + θ_5 * AGE VPD1= EMAX - EMAX * CMIN / (I50 + CMIN) VPD2= VPD1 * θ_3^{TABQ} * θ_4^{TABB} Y = VPD2 * (1 + ϵ_1)	θ_1 = 1.66 (0.438) θ_2 = -5.29 (6.27) θ_3 = 0.996 (0.443) θ_4 = 1.32 (0.561) θ_5 = 0.161 (0.177)	ω_{11} = 0.839 (0.200) σ_{11} = 0.326 (0.0865)	726.384 MRST 3.5 SigDig	[A13] - [A14] = -1.4 Cmin as informative as Cavg
Substitute dose for Cavg in [A13]	[A15] Run 10061008 (APDX) EMAX= θ_1 * AGE * (1 +η_1) I50 = θ_2 + θ_5 * AGE VPD1= EMAX - EMAX * DOSE / (I50 + DOSE) VPD2= VPD1 * θ_3^{TABQ} * θ_4^{TABB} Y = VPD2 * (1 + ϵ_1)	θ_1 = 1.71 (0.451) θ_2 = -150 (481) θ_3 = 2.24 (1.93) θ_4 = 2.53 (2.01) θ_5 = 17.0 (22.0)	ω_{11} = 0.684 (0.161) σ_{11} = 0.371 (0.102)	717.735 MRST 3.6 SigDig	[A9] - [A15] = -0.2 [A13] - [A15] = 7.2 [A14] - [A15] = 8.6 Cavg or Cmin no better than dose as predictor
Dose informative beyond Cavg or Cmin	[A16] Run 10061009 EMAX= θ_1 * AGE * (1 +η_1) I50 = θ_2 + θ_5 * AGE VPD1= EMAX - EMAX * CAVG / (I50 + CAVG) VPD2= VPD1 * θ_3^{TABQ} * θ_4^{TABB} VPD3= VPD2 + θ_6 * DOSE Y = VPD3 * (1 + ϵ_1)	θ_1 = 1.16 (0.378) θ_2 = -0.215 (0.494) θ_3 = 2.76 (4.70) θ_4 = 4.44 (7.69) θ_5 = 0.00840 (0.0191) θ_6 = 0.0127 (0.00457)	ω_{11} = 3.06 (1.90) σ_{11} = 0.437 (0.167)	715.656 MRST 4.4 SigDig	[A13] - [A16] = 9.3 [A14] - [A16] = 10.7 [A15] - [A16] = 2.1 Cavg or Cmin no better than dose as predictor

Table 2. Population Concentration-Effect Modeling of Average VPD Rate (VPDavg) As a Function of Average (Cavg) and Minimum (Cmin) Procainamide Concentrations and Average NAPA (Cavm) Concentration During 12-Hour Steady-State Intervals (74 observations for 42 patients) (Protocol 610-43)

Test/Hypothesis	Model	θ (SE)	ω^2, σ^2 (SE)	Fitting Stats	Conclusions
Emax Models Based on Average NAPA Concentration (Cavm)					
Substitute average NAPA conc (Cavm) for Cavg in [A13]	[A17] Run 7091400 $EMAX = \theta_1 * AGE * (1 + \eta_1)$ $I50 = \theta_2 + \theta_5 * AGE$ $VPD1 = EMAX - EMAX * CAVM / (I50 + CAVM)$ $VPD2 = VPD1 * \theta_3^{TABQ} * \theta_4^{TABB}$ $Y = VPD2 * (1 + \epsilon_1)$	θ_1 = 1.68 (0.443) θ_2 = -2.26 (1.92) θ_3 = 1.46 (0.755) θ_4 = 1.79 (0.918) θ_5 = 0.0719 (0.0580)	ω_{11} = 0.815 (0.230) σ_{11} = 0.313 (0.102)	720.436 MRST 3.1 SigDig	[A13] - [A17] = 4.5 Cavg and Cavm convey similar information.
A linear combination of average NAPA conc (Cavm) and average PA conc (Cavg) is best predictor	[A18] Run 7151400 $EMAX = \theta_1 * AGE * (1 + \eta_1)$ $I50 = \theta_2 * (1 + AGE)$ $CONC = CAVM + \theta_5 * CAVG$ $VPD1 = EMAX - EMAX * CONC / (I50 + CONC)$ $VPD2 = VPD1 * \theta_3^{TABQ} * \theta_4^{TABB}$ $Y = VPD2 * (1 + \epsilon_1)$	θ_1 = 1.66 (0.436) θ_2 = 0.0521 (0.0576) θ_3 = 1.39 (0.739) θ_4 = 1.66 (0.868) θ_5 = 0.268 (1.10)	ω_{11} = 0.854 (0.220) σ_{11} = 0.321 (0.0950)	724.567 MRST 3.7 SigDig	[A13] - [A18] = 0.4 [A17] - [A18] = -4.1 Cavg and Cavm convey similar information.

VPD = Average VPD rate during 12-hour steady-state interval as a percentage of 48-hour average baseline measurement.
Cavg = Average steady-state PA concentration during 12-hour interval [AUC(0-12)/12] (μg/mL).
Cavm = Average steady-state NAPA concentration (μg/mL).
Cmin = Minimum PA concentration during 12-hour interval (μg/mL).
TABB = 1 if BID treatment, 0 otherwise; TABQ = 1 if QID treatment, 0 otherwise.
Fitting Stats = Minimum value of objective function; minimization outcome; number of significant digits in parameter estimates.
MRST = Minimization routine successfully terminated.
APDX = NONMEM output in Appendix F

Table 3. Population Concentration-Effect Modeling of Hourly VPD Rates As a Function of Procainamide Concentration (Cpa) and NAPA Concentration (Cmet) During 12-Hour Steady-State Intervals (960 observations for 42 patients) (Protocol 610-43)

Test/Hypothesis	Model	θ (SE)	ω^2, σ^2 (SE)	Fitting Stats	Conclusions
Linear Models Based on PA concentration (Cpa)					
VPD rate is described by overall mean value $\eta_1 \sim N(0,\omega_{11})$ $\epsilon_1 \sim N(0,\sigma_{11})$	[B1] Run 6300800 $VPD = \theta_1 * (1 + \eta_1)$ $Y = VPD * (1 + \epsilon_1)$	θ_1 = 96.4 (17.2)	ω_{11} = 1.38 (0.329) σ_{11} = 1.16 (0.230)	10011.308 MRST 3.3 SigDig	base model
VPD rate is linear function of age	[B2] Run 9051012 $INT = \theta_1$ $COA = \theta_2 * (1 + \eta_1)$ $VPD = INT + COA * AGE$ $Y = VPD * (1 + \epsilon_1)$	θ_1 = -36.0 (19.4) θ_2 = 2.10 (0.509)	ω_{11} = 0.640 (0.179) σ_{11} = 1.00 (0.189)	9805.863 MRST 3.6 SigDig	age is covariate
VPD rate is linear function of Cpa	[B3] Run 6300801 $INT = \theta_1 * (1 + \eta_1)$ $SLP = \theta_2$ $VPD = INT + SLP * CPA$ $Y = VPD * (1 + \epsilon_1)$	θ_1 = 94.5 (15.5) θ_2 = -5.46 (3.13)	ω_{11} = 1.40 (0.648) σ_{11} = 1.48 (0.710)	9976.537 MRST 3.5 SigDig	[B1] - [B3] = 34.8
Formulation affects linear concentration model; TABQ= 1 if QID, 0 otherwise TABB= 1 if BID, 0 otherwise	[B4] Run 6300802 $INT = \theta_1 * (1 + \eta_1)$ $SLP = \theta_2$ $VPD1 = INT + SLP * CPA$ $VPD2 = VPD1 * \theta_3^{TABQ} * \theta_4^{TABB}$ $Y = VPD2 * (1 + \epsilon_1)$	θ_1 = 52.7 (26.9) θ_2 = -3.70 (1.01) θ_3 = 1.90 (0.546) θ_4 = 2.01 (0.621)	ω_{11} = 2.09 (2.47) σ_{11} = 1.63 (1.61)	9849.436 MRST 3.4 SigDig	[B3] - [B4] = 127.1 formulation index is important; VPD rate high for QID and BID at low conc.
Age affects slope of linear model	[B5] Run 7051400 $INT = \theta_1 * (1 + \eta_1)$ $SLP = \theta_2 + \theta_5 * AGE$ $VPD1 = INT + SLP * CPA$ $VPD2 = VPD1 * \theta_3^{TABQ} * \theta_4^{TABB}$ $Y = VPD2 * (1 + \epsilon_1)$	θ_1 = 30.9 (5.26) θ_2 = -24.1 (3.17) θ_3 = 1.64 (0.481) θ_4 = 1.81 (0.509) θ_5 = 0.362 (0.0467)	ω_{11} = 8.13 (4.98) σ_{11} = 4.66 (2.06)	9745.755 MRST 3.8 SigDig	[B4] - [B5] = 103.7 age is covariate

Table 3. Population Concentration-Effect Modeling of Hourly VPD Rates As a Function of Procainamide Concentration (Cpa) and NAPA Concentration (Cmet) During 12-Hour Steady-State Intervals (960 observations for 42 patients) (Protocol 610-43)

Test/Hypothesis	Model	θ (SE)	ω^2, σ^2 (SE)	Fitting Stats	Conclusions
Concentration and age effects are additive; $\eta_2 \sim N(0,\omega_{22})$	[B6] Run 9061107 INT = θ_1 SLP = $\theta_2 * (1 + \eta_1)$ COA = $\theta_3 * (1 + \eta_2)$ VPD = INT + SLP * CPA + COA * AGE Y = VPD * $(1 + \epsilon_1)$	θ_1 = -36.2 (16.7) θ_2 = - 7.17 (2.46) θ_3 = 2.06 (0.482)	ω_{11} = 22.7 (22.9) ω_{12} = 4.54 (3.46) ω_{22} = 1.07 (0.543) σ_{11} = 1.37 (0.406)	9709.325 MRST 3.3 SigDig	[B5] - [B6] = 36.4 variances large
Formulation affects additive model	[B7] Run 9061106 (APDX) INT = θ_1 SLP = $\theta_2 * (1 + \eta_1)$ COA = $\theta_5 * (1 + \eta_2)$ VPD1 = INT + SLP * CPA + COA * AGE VPD2 = VPD1 * $\theta_3^{TABQ} * \theta_4^{TABB}$ Y = VPD2 * $(1 + \epsilon_1)$	θ_1 = -14.8 (13.0) θ_2 = -5.47 (1.37) θ_3 = 1.55 (0.435) θ_4 = 1.63 (0.457) θ_5 = 1.25 (0.374)	ω_{11} = 23.0 (18.5) ω_{12} = 5.90 (3.66) ω_{22} = 1.69 (0.838) σ_{11} = 1.44 (0.476)	9652.553 MRST 4.3 SigDig	[B6] - [B7] = 56.8 best linear model, but variances large
Emax Models Based on PA concentration (Cpa)					
VPD rate is related to Cpa by inhibitory Emax model. Emax constrained to equal baseline.	[B8] Run 9051008 Emax = $\theta_1 * (1 + \eta_1)$ I50 = θ_2 VPD = EMAX - EMAX * CPA / (I50 + CPA) Y = VPD * $(1 + \epsilon_1)$	θ_1 = 107 (24.4) θ_2 = 11.5 (11.1)	ω_{11} = 1.29 (0.277) σ_{11} = 1.20 (0.247)	9977.584 MRST 3.2 SigDig	comparable to [B3]
Sigmoidal inhibitory Emax model	[B9] Run 7151040 EMAX = $\theta_1 * (1 + \eta_1)$ I50 = θ_2 SIGM = θ_3 A = CPA ** SIGM B = I50 ** SIGM VPD = EMAX - EMAX * A / (B + A) Y = VPD * $(1 + \epsilon_1)$	θ_1 = 105 (22.3) θ_2 = 9.34 (7.08) θ_3 = 1.40 (0.492)	ω_{11} = 1.27 (0.267) σ_{11} = 1.19 (0.245)	9971.802 MRST 4.2 SigDig	[B8] - [B9] = 5.8 complexity of sigmoidicity not justified

Table 3. Population Concentration-Effect Modeling of Hourly VPD Rates As a Function of Procainamide Concentration (Cpa) and NAPA Concentration (Cmet) During 12-Hour Steady-State Intervals (960 observations for 42 patients) (Protocol 610-43)

Test/Hypothesis	Model	θ (SE)	ω^2, σ^2 (SE)	Fitting Stats	Conclusion
Formulation affects inhibitory Emax model	[B10] Run 6300901 $EMAX = \theta_1 * (1 + \eta_1)$ $I50 = \theta_2$ $VPD1 = EMAX - EMAX * CPA / (I50 + CPA)$ $VPD2 = VPD1 * \theta_3^{TABQ} * \theta_4^{TABB}$ $Y = VPD2 * (1 + \epsilon_1)$	θ_1 = 70.1 (13.7) θ_2 = 4.31 (3.83) θ_3 = 2.37 (0.984) θ_4 = 2.43 (1.00)	ω_{11} = 1.18 (0.239) σ_{11} = 0.904 (0.160)	9817.562 MRST 3.2 SigDig	[B8] - [B10] = 163.0 [B4] - [B10] = 31.9 formulation index is important; VPD rate high for QID and BID at low conc; superior to corresponding linear model
Age effect is additive	[B11] Run 9051015 $EMAX = \theta_1 * (1 + \eta_1)$ $I50 = \theta_2$ $COA = \theta_5 * (1 + \eta_2)$ $VPD1 = EMAX - EMAX * CPA / (I50 + CPA)$ $VPD2 = VPD1 * \theta_3^{TABQ} * \theta_4^{TABB}$ $VPD3 = VPD2 + COA * AGE$ $Y = VPD3 * (1 + \epsilon_1)$	θ_1 = 3.92 (10.1) θ_2 = 0.0436 (0.106) θ_3 = 20.9 (24.8) θ_4 = 246 (554) θ_5 = 0.953 (0.410)	ω_{11} = 4.43 (6.91) ω_{12} = -2.75 (1.95) ω_{22} = 4.34 (4.83) σ_{11} = 1.30 (0.551)	9737.607 MRST 3.1 SigDig	[B7] - [B11] = -85.1 [B10] - [B11] = 80.0 large variances; model sensitive to starting values
Effect of age is on Emax alone; I50 varies between patients	[B12] Run 9051017 $TEMAX = \theta_1 + \theta_5 * AGE$ $EMAX = TEMAX * (1 + \eta_1)$ $I50 = \theta_2 * (1 + \eta_2)$ $VPD1 = EMAX - EMAX * CPA / (I50 + CPA)$ $VPD2 = VPD1 * \theta_3^{TABQ} * \theta_4^{TABB}$ $Y = VPD2 * (1 + \epsilon_1)$	θ_1 = -13.5 (13.8) θ_2 = 4.40 (3.32) θ_3 = 1.83 (0.698) θ_4 = 1.89 (0.698) θ_5 = 1.13 (0.448)	ω_{11} = 5.55 (4.26) ω_{12} = -14.5 (11.1) ω_{22} = 43.4 (35.9) σ_{11} = 1.68 (0.718)	9656.583 MRST 3.6 SigDig	[B10] - [B12] = 161.0 [B11] - [B12] = 81.0 age affects Emax
Age affects Emax and I50	[B13] Run 7050804 (APDX) $EMAX = \theta_1 * AGE * (1 + \eta_1)$ $I50 = \theta_2 + \theta_5 * AGE$ $VPD1 = EMAX - EMAX * CPA / (I50 + CPA)$ $VPD2 = VPD1 * \theta_3^{TABQ} * \theta_4^{TABB}$ $Y = VPD2 * (1 + \epsilon_1)$	θ_1 = 1.25 (0.269) θ_2 = -3.92 (3.98) θ_3 = 1.99 (0.760) θ_4 = 2.03 (0.758) θ_5 = 0.130 (0.116)	ω_{11} = 1.08 (0.222) σ_{11} = 0.859 (0.161)	9655.109 MRST 4.8 SigDig	[B5] - [B13] = 90.6 [B7] - [B13] = -2.6 [B11] - [B13] = 24.8 [B12] - [B13] = 1.5 age and formulation index are both important; best Emax model; superior to linear model

Table 3. Population Concentration-Effect Modeling of Hourly VPD Rates As a Function of Procainamide Concentration (Cpa) and NAPA Concentration (Cmet) During 12-Hour Steady-State Intervals (960 observations for 42 patients) (Protocol 610-43)

(Page 4 of 5)

Test/Hypothesis	Model	θ (SE)	ω^2, σ^2 (SE)	Fitting Stats	Conclusion
Intersubject variability high for 1000-mg dose group	[B14] Run 9051002 TEMAX = θ_1 * AGE EMA1 = TEMAX * (1 + η_1) EMA2 = TEMAX * (1 + η_2) Q = 1 IF (DOSE.EQ.1000) Q = 0 EMAX = Q * EMAX1 + (1-Q) * EMAX2 I50 = θ_2 + θ_5 * AGE VPD1 = EMAX - EMAX * CPA / (I50 + CPA) VPD2 = VPD1 * θ_3^{TABQ} * θ_4^{TABB} Y = VPD2 * (1 + ϵ_1)	θ_1 = 1.25 (0.264) θ_2 = -3.95 (3.97) θ_3 = 1.98 (0.737) θ_4 = 2.01 (0.743) θ_5 = 0.131 (0.116)	ω_{11} = 1.03 (0.254) ω_{22} = 1.28 (0.541) σ_{11} = 0.868 (0.161)	9654.940 MRST 3.6 SigDig	[B13] - [B14] = 0.2 complexity not justified
Emax Models Based on NAPA Concentration (Cmet)					
VPD rate is related to NAPA conc by inhibitory Emax model. Emax constrained to equal baseline.	[B15] Run 7131025 EMAX = θ_1 * (1 + η_1) I50 = θ_2 VPD = EMAX - EMAX * CMET / (I50 + CMET) Y = VPD * (1 + ϵ_1)	θ_1 = 116 (15.9) θ_2 = 7.23 (1.09)	ω_{11} = 1.31 (0.386) σ_{11} = 1.19 (0.196)	9960.806 MRST 3.5 SigDig	[B8] - [B15] = 17.1 analogous to procainamide Model B8
Formulation affects inhibitory Emax model	[B16] Run 7121530 EMAX = θ_1 * (1 + η_1) I50 = θ_2 VPD1 = EMAX - EMAX * CMET / (I50 + CMET) VPD2 = VPD1 * θ_3^{TABQ} * θ_4^{TABB} Y = VPD2 * (1 + ϵ_1)	θ_1 = 73.0 (14.5) θ_2 = 1.78 (1.40) θ_3 = 3.50 (1.81) θ_4 = 3.35 (1.80)	ω_{11} = 1.17 (0.259) σ_{11} = 0.826 (0.150)	9747.662 MRST 3.7 SigDig	[B15] - [B16] = 212.8 formulation index important

Table 3. Population Concentration-Effect Modeling of Hourly VPD Rates As a Function of Procainamide Concentration (Cpa) and NAPA Concentration (Cmet) During 12-Hour Steady-State Intervals (960 observations for 42 patients) (Protocol 610-43)

(Page 5 of 5)

Test/Hypothesis	Model	θ (SE)	ω^2, σ^2 (SE)	Fitting Stats	Conclusion
Formulation index and age covariate are both important	[B17] Run 7121500 (APDX) EMAX = θ_1 * AGE * (1 + η_1) I50 = θ_2 + θ_5 * AGE VPD1 = EMAX - EMAX * CMET / (I50 + CMET) VPD2 = VPD1 * θ_3^{TABQ} * θ_4^{TABB} Y = VPD2 * (1 + ϵ_1)	θ_1 = 1.30 (0.270) θ_2 = -1.11 (0.789) θ_3 = 3.61 (1.79) θ_4 = 3.37 (1.72) θ_5 = 0.0360 (0.0246)	ω_{11} = 1.02 (0.222) σ_{11} = 0.787 (0.136)	9535.968 MRST 3.6 SigDig	[B16] - [B17] = 211.7 [B13] - [B17] = 119.1 best model of NAPA conc; Cmet may be more informative than Cpa
A linear combination of Cpa and Cmet	[B18] Run 7151002 EMAX = θ_1 * AGE * (1 + η_1) I50 = θ_2 * (1 + AGE) CONC = CMET + θ_5 * CPA VPD1 = EMAX - EMAX * CONC / (I50 + CONC) VPD2 = VPD1 * θ_3^{TABQ} * θ_4^{TABB} Y = VPD2 * (1 + ϵ_1)	θ_1 = 1.29 (0.276) θ_2 = 0.0196 (0.0156) θ_3 = 3.48 (1.91) θ_4 = 3.15 (1.76) θ_5 = -0.0168 (0.409)	ω_{11} = 1.08 (0.233) σ_{11} = 0.794 (0.143)	9586.851 MRST 3.7 SigDig	[B13] - [B18] = 68.2 [B17] - [B18] = -50.9 Cmet may be more informative than Cpa

VPD = Hourly VPD rate (counts/1.0 hr) as a percentage of 48-hour average baseline measurement.
CPA = Procainamide (PA) concentration (μg/mL).
CMET = N-acetylprocainamide (NAPA) concentration (μg/mL).
TABB = 1 if BID treatment, 0 otherwise; TABQ = 1 if QID treatment, 0 otherwise.
Fitting Stats = Minimum value of objective function; minimization outcome; number of significant figures in parameter estimates.
MRST = Minimization routine successfully terminated.
APDX = NONMEM output in Appendix F.

Study 7: Bioequivalence of PROCANBID 1000-mg tablets at steady-state as compared to formulation used in clinical program.

Study Title: A multiple-dose bioequivalence study in healthy subjects comparing market-image 1000-mg Procainamide BID tablets to 1000-mg Procainamide BID tablets used in a multicenter clinical trial (Protocol 610-51).

Study Number: RR-744-00164

Volume Number: 1.18

Objectives: To determine whether market-image 1000-mg PROCANBID tablets are bioequivalent to the 1000-mg PROCANBID formulation used in a multicenter clinical study.

Design: Open, randomized, multi-dose, two-way crossover study.

Treatments: Healthy subjects were randomized into 1 of 2 treatment sequences. On two occasions, 1 week apart, each subject received one 1000-mg PROCANBID tablet of either the market image (Formulation 46A2, test treatment) or the clinical trial formulation (46A1, reference treatment) every 12 hours for 7 doses. Subjects were required to fast 8 hours prior to each morning dose and for 4 hours following the final dose of each treatment.

Formulation	% Dissolved		
	1 hr	6 hr	12 hr
W8213A-46A1, Lot CM 064030, reference treatment	13	56	78
W8213A-46A2, Lot CM 1251093, test treatment	11	51	75

Subjects: The age of the 24 healthy subjects was 21-50 years (mean 35 years). Seven were females. 20 were white, 3 were black and one was Asian. Six of the subjects were smokers.

Blood Sampling and Assay: Plasma samples were collected before, treatment and at 24, 48, 60, 72, 72.5 73, 73.5, 74, 75, 76, 76.5, 77, 78, 80, 82, and 84 hours after the initial dose of each treatment. Samples were analyzed for procainamide and NAPA.

Statistical Evaluation: The statistical evaluation followed FDA guidelines. The bioequivalence was based on evaluating log-transformed data of C_{max} and AUC during a dosage interval. The two one-sided test procedure was used to establish confidence

interval for bioequivalence.

STUDY RESULTS:

Plasma concentration profiles: The mean plasma concentration profiles during steady-state for procainamide and NAPA were virtually superimposable for the two formulations (see Figure 1). The pharmacokinetic parameters are presented in Table 1 for procainamide and Table 2 for NAPA.

Bioequivalence evaluation: The 90% confidence intervals for C_{max} and $AUC_{72\text{-}84\ hr}$ (see Tables 1 and 2) demonstrate that the two formulations are bioequivalent.

Table 1. Pharmacokinetic parameters for procainamide, mean (%CV), during steady-state following multiple doses of 1000-mg PROCANBID final market image (test) and 1000-mg PROCANBID tablets used in clinical trials (reference).

Parameter	Market Image (test)	Clinical Tablet (ref.)	Test/Ref	90% Confidence interval
C_{max} (mg/L)	2.17 (32%)	2.16 (36%)	1.01	96-107
T_{max} (hr)	3.5 (30%)	3.4 (32%)	1.03	-
AUC(72-84) (mg*hr/L)	18.4 (33%)	18.6 (37%)	0.99	94-106
C_{min} (mg/L)	0.96 (44%)	0.92 (49%)	1.04	94-119
$(C_{max} - C_{min})/C_{min}$	0.83 (35%)	0.84 (35%)	0.99	88-109

Table 2. Pharmacokinetic parameters for NAPA, mean (%CV), during steady-state following multiple doses of 1000-mg PROCANBID final market image (test) and 1000-mg PROCANBID tablets used in clinical trials (reference).

Parameter	Market Image (test)	Clinical Tablet (ref.)	Test/Ref	90% Confidence interval
C_{max} (mg/L)	1.59 (44%)	1.59 (41%)	1.00	95-104
T_{max} (hr)	3.9 (40%)	4.1 (43%)	0.95	-
AUC(72-84) (mg*hr/L)	16.1 (44%)	15.8 (39%)	1.02	97-104
C_{min} (mg/L)	1.11 (49%)	1.08 (45%)	1.03	96-108
$(C_{max} - C_{min})/C_{min}$	0.37 (36%)	0.39 (37%)	0.95	84-105

Conclusions: The PROCANBID 1000-mg market image formulation is bioequivalent with the PROCANBID 1000-mg formulation that was used in a multicenter clinical trial.

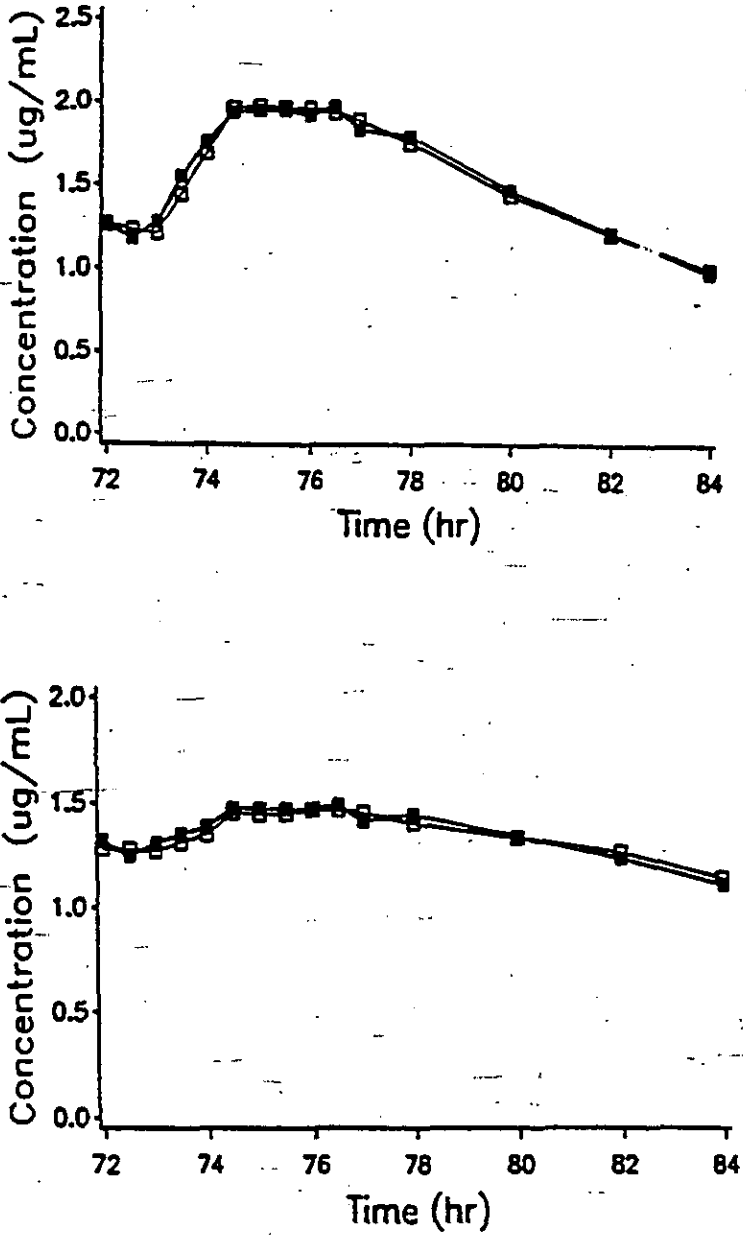


Figure 1. Mean plasma concentration profiles of
a) procainamide (upper panel)
b) NAPA (lower panel)
following the final dose of multiple-dose administration of one 1000-mg PROCANBID Market-Image formulation (open symbols) twice daily with one 1000-mg PROCANBID reference formulation (filled symbols) twice daily.

Study 8: Dose proportionality of market image; a single-dose study.

Study Title: A single-dose, dose-proportionality study in healthy subjects comparing market-image 500-, 750-, and 1000-mg Procainamide BID tablet formulations (Protocol 610-52).

Study Number: RR-744-00165

Volume Number: 1.19

Objectives: Determine whether plasma procainamide concentrations are dose-proportional following administration of market-image 500-, 750-, and 1000-mg tablet formulations.

Design: Open, randomized, single-dose, three-way crossover study.

Treatments: On 3 occasions, 1 week apart, each subject received a single 500-, 750-, or 1000-mg tablet (see table below). Subjects fasted 8 hours prior to the morning dose and for 4 hours following the dose, except 6 ounces of unsweetened juice after 2 hours.

Formulation	% Dissolved		
	1 hr	6 hr	12 hr
500-mg W8213A-47A2, Lot CM 1271093			
750-mg W8213A-53A1, Lot CM 1261093			
1000-mg W8213A-46A2, Lot CM 1251093			

Subjects: The age of the 23 healthy subjects who concluded the study was 21-52 years (mean 33 years). 18 were females. 21 subjects were white, and 2 were black.

Blood Sampling and Assay: Serial plasma samples were collected before treatment and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours following dosing. Samples were analyzed for procainamide and NAPA.

Pharmacokinetic and Statistical Evaluation: Noncompartmental analysis was performed. All C_{max} and AUC values were normalized to a 1000-mg dose (nC_{max} and AUC). Dose proportionality was assessed by inspection of ratios of individual and mean dose-normalized

parameters and corresponding 90% confidence intervals using that the 1000-mg tablet as reference. Log-transformed nC_{max} and nAUC values were evaluated with ANOVA and 90% confidence intervals were determined using the two one-sided test procedure. AUC_{∞} was considered a less reliable parameter than the AUC(0-tldc) (area to the last detectable concentration) because of uncertainty in determination of the extrapolated area. Hence only AUC(0-tldc) was used for statistical evaluations.

STUDY RESULTS:

Plasma concentration profiles: The mean plasma concentration profiles for procainamide and NAPA are presented in Figure 1. From these curves it appears that the difference between the 750-mg and the 1000-mg tablets is much smaller than the difference between the 500-mg and the 750-mg tablets. The pharmacokinetic parameters, support this impression (see Table 1 for procainamide and Table 2 for NAPA).

Evaluation of dose-proportionality: The 90% confidence intervals for nC_{max} of the 500-mg tablet as compared to the 1000-mg tablet was 94-104% (see Tables 1 and 2) demonstrating that the two formulations are dose-proportional. The nAUC(0-tldc) for the 500-mg tablet was 11% higher than that for the 1000-mg tablet with a confidence interval of 95-128%. This indicates only a minor deviation from dose-proportionality.

In contrast, the procainamide data for the 750-mg tablet indicates large deviations from dose-proportionality both when compared with the 1000-mg tablet (see Table 2) and when compared to the 500-mg tablet (for confidence limits see submission). Hence dose-proportionality could not be shown. The evaluation of NAPA parameters confirmed the evaluation of the procainamide parameters.

Table 1. Pharmacokinetic parameters for procainamide, mean (%CV), following a single dose of 500-mg PROCANBID formulation 47A2 (test) and 1000-mg PROCANBID formulation 46A2 (reference).

Parameter	500-mg tablet (test)	1000-mg tablet (reference)	Test/Ref (dose-normalized data)	90% Confidence Interval
C_{max} (mg/L)	0.61 (24%)	1.26 (29%)	0.97	94-104
AUC(0-tldc) (mg*hr/L)	7.6 (46%)	13.5 (46%)	1.13	95-128
T_{max} (hr)	4.0 (26%)	4.4 (28%)	0.91	-

Table 2. Pharmacokinetic parameters for procainamide, mean (%CV), following a single dose of 750-mg PROCANBID formulation 53A1 (test) and 1000-mg PROCANBID formulation 46A2 (reference).

Parameter	750-mg tablet (test)	1000-mg tablet (reference)	Test/Ref (dose-normalized data)	90% Confidence Interval
C_{max} (mg/L)	1.15 (23%)	1.26 (29%)	1.22	116-129
AUC(0-tldc) (mg*hr/L)	13.3 (34%)	13.5 (46%)	1.31	118-158
T_{max} (hr)	3.7 (28%)	4.4 28%)	0.84	-

Discussion: The present study was undertaken with the three strengths of the market image tablet for which the firm was going to ask for approval. The *in vitro* dissolution rate of the 750-mg formulation was higher than that of the two other formulations, which explains the failure to show dose-proportionality for C_{max}. It is more difficult to understand that AUC(0-tldc) failed, since the rate of dissolution is not expected to influence the extent of absorption for a drug which is essentially complete absorbed. It is possible that AUC(0-tldc) is not a good choice as a test parameter for extent in this case, and that the results of a steady-state study might have come out different. The results with regard to rate of absorption are unequivocal, however, and demonstrate that the 750-mg formulation behaves quite differently from the other two formulations *in vivo*. Accordingly, based on the results of the present study, the firm decided not to ask for approval for the 750-mg formulation.

Conclusion: The 500-mg and 1000-mg formulations, but not the 750-mg formulation, behaved in a dose-proportional manner. The firm is not asking for approval of the latter strength.

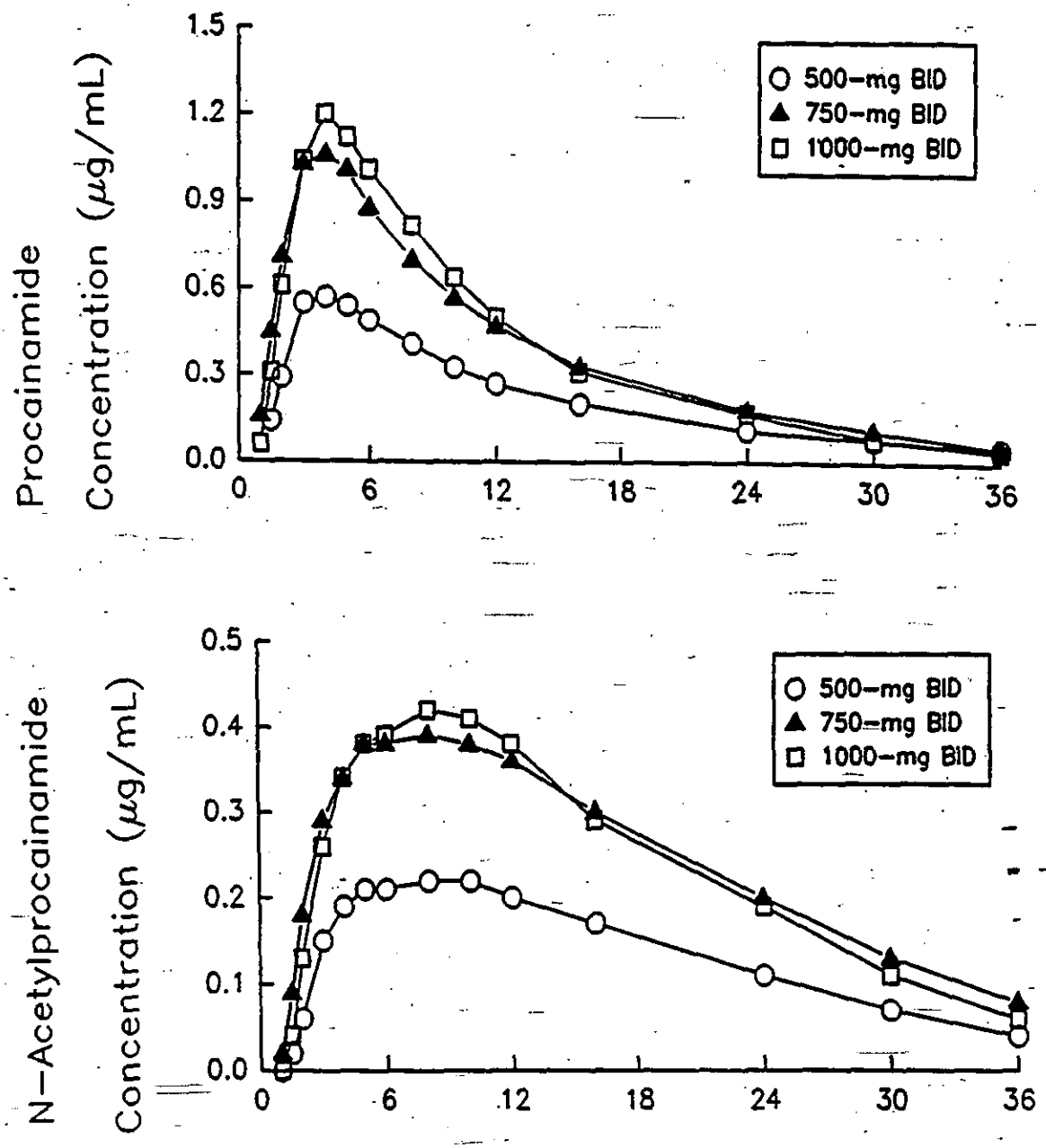


Figure 1. Mean plasma concentration profiles for procainamide (upper panel) and NAPA (lower panel) following administration of one 500-, 750-, and 1000-mg Market-Image PROCANBID tablet.

Study 9: Bioequivalence of PROCANBID 500-mg tablets at steady-state as compared to formulation used in clinical program.

Study Title: A multiple-dose bioequivalence study in healthy subjects comparing market-image 500-mg Procainamide BID tablets to 500-mg Procainamide BID tablets used in a multicenter clinical trial (Protocol 610-53).

Study Number: RR-744-00166

Volume Number: 1.20

Objectives: To determine whether market-image 500-mg PROCANBID tablets are bioequivalent to the 500-mg PROCANBID formulation used in a multicenter clinical trial.

Design: Open, randomized, multi-dose, two-way crossover study.

Treatments: Subjects were randomized into 1 of 2 treatment sequences. On two occasions, 1 week apart, each subject received one 500-mg PROCANBID tablet of either the market image (test treatment) or the clinical trial formulation (reference treatment) every 12 hours for 7 doses. Subjects were required to fast 8 hours prior to each morning dose and for 4 hours following the final dose of each treatment.

Formulation	% Dissolved		
	1 hr	6 hr	12 hr
W8213A-60, Lot CM 230070, reference treatment			
W8213A-47A2,Lot CM 1271093			

Subjects: The age of the 24 healthy subjects was 22-54 years (mean 35 years). Seven were females. 20 were white, 3 were black and 1 was Asian. Four of the subjects were smokers.

Blood Sampling and Assay: Plasma samples were collected before, treatment and at 24, 48, 60, 72, 72.5 73, 73.5, 74, 75, 76, 76.5, 77, 78, 80, 82, and 84 hours after the initial dose of each treatment. Samples were analyzed for procainamide and NAPA.

Statistical Evaluation: The statistical evaluation followed FDA guidelines. The bioequivalence was based on evaluating log-transformed data of C_{max} and AUC during a dosage interval. The two one-sided test procedure was used to establish confidence interval for bioequivalence.

STUDY RESULTS:

Plasma concentration profiles: The mean plasma concentration profiles during steady-state for procainamide and NAPA were higher and appeared to peak earlier for the market formulation than for the formulation used in the clinical trials (see Figure 1). The pharmacokinetic parameters, such as C_{max} and $AUC_{72\text{-}84\ hr}$ seem to support this impression (see Table 1 for procainamide and Table 2 for NAPA).

Bioequivalence evaluation: The 90% confidence intervals for C_{max} and $AUC_{72\text{-}84\ hr}$ (see Tables 1 and 2) demonstrate that the two formulations are bioequivalent.

Table 1. Pharmacokinetic parameters for procainamide, mean (%CV), during steady-state following multiple doses of 500-mg PROCANBID final market image (test) and 500-mg PROCANBID tablets used in clinical trials (reference).

Parameter	Market Image (test)	Clinical Tablet (ref.)	Test/Ref	90% Confidence interval
C_{max} (mg/L)	1.17 (32%)	1.02 (39%)	1.15	108-125*)
T_{max} (hr)	3.7 (29%)	4.4 (33%)	0.84	-
AUC(72-84) (mg*hr/L)	10.3 (33%)	9.27 (41%)	1.11	103-116
C_{min} (mg/L)	0.54 (44%)	0.53 (52%)	1.02	87-118
$(C_{max} - C_{min})/C_{min}$	0.76 (33%)	0.69 (42%)	1.10	101-131

*) The Sponsor reported 107-126%. However, my recalculation of the ANOVA and the two one-sided test procedure gave the result above, indicating bioequivalence. In all other instances I have been able to confirm the results of the Sponsor.

Table 2. Pharmacokinetic parameters for NAPA, mean (%CV), during steady-state following multiple doses of 500-mg PROCANBID final market image (test) and 500-mg PROCANBID tablets used in clinical trials (reference).

Parameter	Market Image (test)	Clinical Tablet (ref.)	Test/Ref	90% Confidence interval
C_{max} (mg/L)	0.696 (56%)	0.598 (54%)	1.16	107-121
T_{max} (hr)	4.5 (33%)	5.1 (56%)	0.88	-
AUC(72-84) (mg*hr/L)	7.24 (58%)	6.31 (55%)	1.15	105-118
C_{min} (mg/L)	0.495 (63%)	0.433 (59%)	1.14	101-119
$(C_{max} - C_{min})/C_{min}$	0.353 (40%)	0.328 (41%)	1.08	92-130

Discussion: The test formulation had a slightly higher *in vitro* release rate than the reference formulation. *In vivo*, the test formulation appeared to have a faster release rate; however, it did pass the bioequivalence criteria both with regard to the parent drug and the active metabolite. The present design, using a multiple-dose administration, precluded a more in depth evaluation of possible differences in rate of absorption between the two formulations.

Conclusions: The PROCANBID 500-mg market image formulation is bioequivalent with the PROCANBID 500-mg formulation that was used in a multicenter clinical trial.

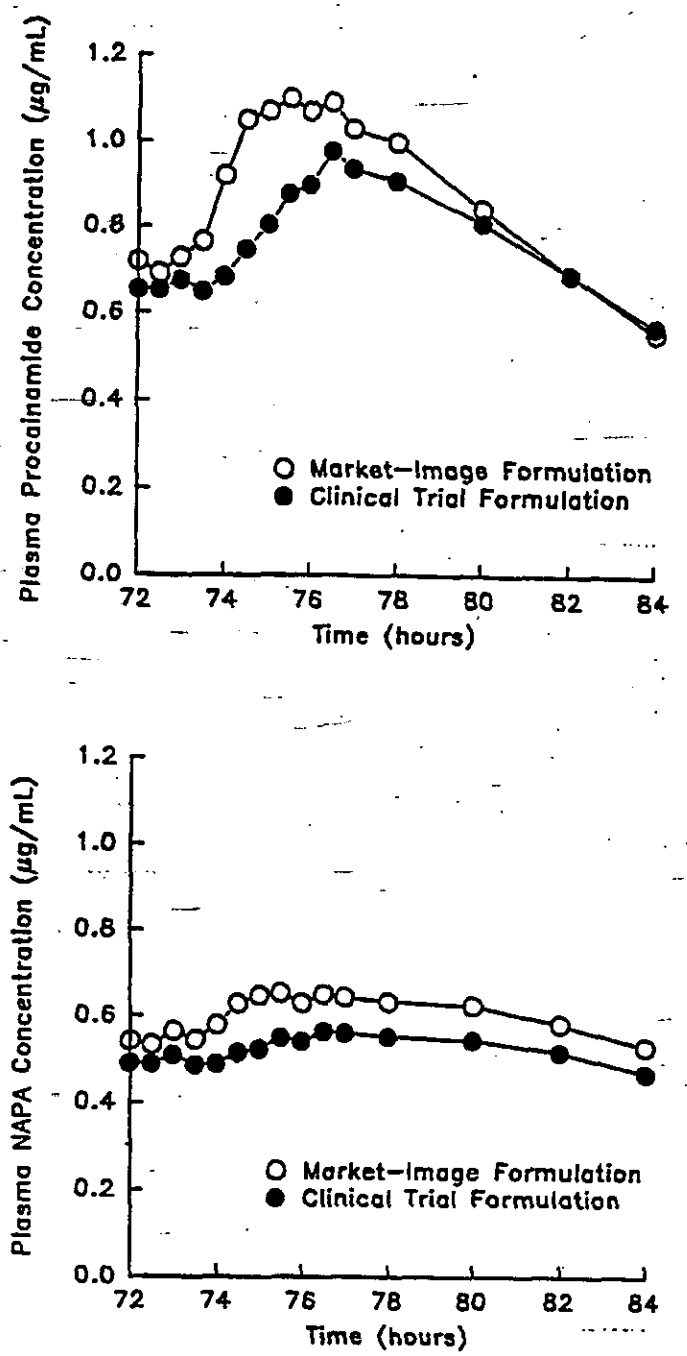


Figure 1. Mean plasma concentration profiles of
a) procainamide (upper panel)
b) NAPA (lower panel)
following the final dose of multiple-dose administration of one 500-mg PROCANBID Market-Image formulation (open symbols) twice daily with one 500-mg PROCANBID reference formulation (filled symbols) twice daily.

Study 10: Dosage strength bioequivalence between 500- and 1000-mg tablets; a multiple-dose study.

Study Title: A multiple-dose, dose-proportionality study in healthy subjects of market-image 500- and 1000-mg Procainamide BID tablet formulations (Protocol 610-54).

Study Number: RR-744-00169

Volume Number: 1.21

Objectives: Determine whether market-image 500- and 1000-mg tablets are bioequivalent when administered in equivalent doses.

Design: Open, randomized, multi-dose, two-way crossover study.

Treatments: On 2 occasions, 1 week apart, each subject received 2 x 500-mg procainamide tablets, or 1 x 1000-mg procainamide tablet (see table below) every 12 hours for 7 doses. Subjects fasted 8 hours prior to each morning dose and for 4 hours following the final dose of each treatment.

Formulation	% Dissolved		
	1 hr	6 hr	12 hr
500-mg W8213A-47A2, Lot CM 1271093 (test)			
1000-mg W8213A-46A2, Lot CM 1251093 (ref.)			

Subjects: The age of the 24 healthy subjects was 22-48 years (mean 34 years). 16 were females. 22 were white, and 2 were black. Three were smokers.

Blood Sampling and Assay: Plasma samples were collected before treatment and at 24, 48, 60, 72, 72.5 73, 73.5, 74, 75, 76, 76.5, 77, 78, 80, 82, and 84 hours after the initial dose of each treatment. Samples were analyzed for PA and NAPA.

Pharmacokinetic and Statistical Evaluation: Noncompartmental analysis was performed. Dose proportionality was assessed by inspection of ratios of individual and mean dose-normalized parameters and corresponding 90% confidence intervals. The latter were based on evaluation of log-transformed parameters, and bioequivalence was declared if confidence limits for the test mean value fell within 80-125% of the reference mean value.

STUDY RESULTS:

Plasma concentration profiles: The mean plasma concentration profiles for procainamide and NAPA, presented in Figure 1, were very similar, and so were mean values for C_{max} and $AUC_{72\text{-}84\ hr}$.

Bioequivalence evaluation: The 90% confidence intervals for C_{max} and $AUC_{72\text{-}84\ hr}$ of procainamide (see Table 1) demonstrate that the two formulations, when given at the same total daily dose, are bioequivalent. The evaluation of NAPA gave the same result (Table 2)

Table 1. Pharmacokinetic parameters for procainamide, mean (%CV), during steady-state following multiple doses of 2 x 500-mg PROCANBID final market image (test) and 1000-mg PROCANBID tablets (reference).

Parameter	2 x 500 mg (test)	1000 mg (ref.)	Test/Ref	90% Confidence interval
C_{max} (mg/L)	2.60 (28%)	2.53 (25%)	1.03	95-109
T_{max} (hr)	4.6 (24%)	3.8 (24%)	1.21	-
$AUC_{72\text{-}84\ hr}$ (mg*hr/L)	23.3 (26%)	22.1 (25%)	1.05	97-112
C_{min} (mg/L)	1.32 (29%)	1.20 (33%)	1.10	100-122
$(C_{max} - C_{min})/C_{min}$	0.668 (29%)	0.736 (27%)	0.91	82-99

Table 2. Pharmacokinetic parameters for NAPA, mean (%CV), during steady-state following multiple doses of 2 x 500-mg PROCANBID final market image (test) and 1000-mg PROCANBID tablets (reference).

Parameter	2 x 500 mg (test)	1000 mg (ref.)	Test/Ref	90% Confidence interval
C_{max} (mg/L)	1.29 (30%)	1.35 (35%)	0.96	92-104
T_{max} (hr)	4.9 (57%)	5.0 (42%)	0.98	-
$AUC_{72\text{-}84\ hr}$ (mg*hr/L)	13.7 (30%)	13.8 (36%)	0.99	95-107
C_{min} (mg/L)	0.97 (33%)	0.95 (38%)	1.02	97-111
$(C_{max} - C_{min})/C_{min}$	0.288 (35%)	0.353 (31%)	0.82	72-92

Conclusion: Maintenance treatments with 2 x 500-mg PROCANBID b.i.d. or 1 x 1000-mg PROCANBID b.i.d. are bioequivalent.

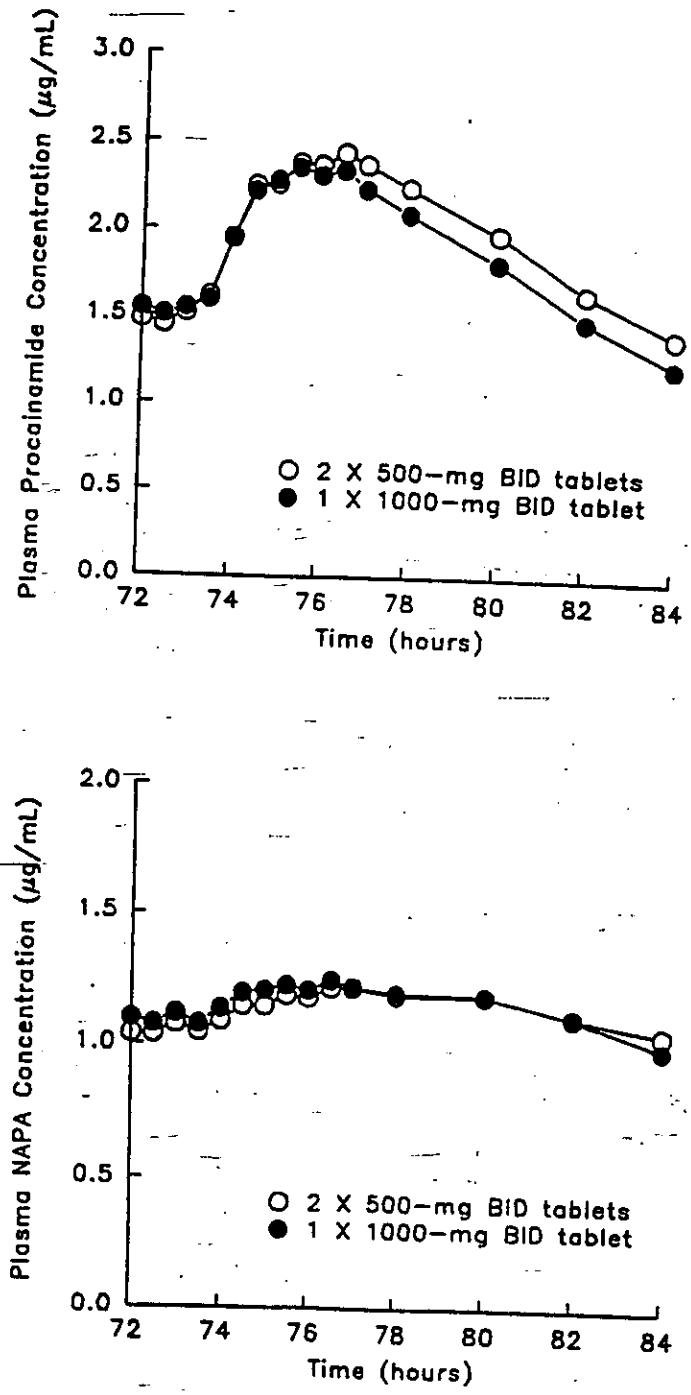


Figure 1. Mean plasma concentration profiles for procainamide (upper panel) and NAPA (lower panel) following the final dose of multiple-dose administration of 2 x 500-mg PROCANBID and 1 x 1000-mg PROCANBID.

APPENDIX 3
COPY OF PROPOSED PACKAGE INSERT

Redacted 37

pages of trade

secret and/or

confidential

commercial

information