CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-438

Medical Review(s)

Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
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Memorandum

DATE: 8.30.02

FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

SUBJECT: NDA 21-438
NAME OF DRUG: Propanolol extended release, — (initial proposed name, —
SPONSOR: Reliant Pharmaceuticals, LLC

DOCUMENTS USED FOR MEMO:

1. Medical Reviews by Maryann Gordon, M.D., dated 5.1.02, 8.5.02 respectively.
2. Secondary Medical Review by Avi Karkowsky, M.D., dated 8.08.02.
3. Chemistry Reviews by Stuart Zimmerman, Ph.D., dated 8.16.02 and 8.16.02 (Reviews #1 and 2 respectively).
4. Clinical Pharmacology and Biopharmaceutics Review by Angelica Dorantes, Pharm.D., dated 8.09.02.
5. Statistical Review of Clinical Data by Yong-Cheng Wang, Ph.D., dated 5.08.02.
6. Proprietary Name review by Hye-Joo Kim, Division of Medication Errors and Technical Support (DMETS), dated 7.12.02. — was viewed as acceptable.
7. Fax from the sponsor dated 8.23.02 regarding the dose-dependence of the anti-hypertensive effects of —
8. Proposed — labeling and comments on labeling by Dr. Karkowsky.
9. Supplemental NDA for Inderal LA, NDA 18-553.

CONCLUSIONS

This memorandum constitutes the Divisional memorandum decision of an approvable action for the NDA named above for — as an antihypertensive at doses of 80 and 120 mg given once per day at night. No indications for — can be granted without additional data in the form of a successful demonstration of —

BACKGROUND AND OVERVIEW

The clinical reviewers all agree that — lowers blood pressure. There are two remaining issues: the dose-response for — over the range of doses studied, and the duration of the antihypertensive effect of — (put another way, the appropriate inter-dosing interval for this formulation). These issues shouldn't be hard to resolve given the amount of PK data available for — from the healthy volunteer studies. Here, the AUC and Cmax of the various doses of — were dose-proportional between 80 and 640 mg and the PK profile of propanolol in — is similar to that of Inderal LA (an approved drug with once per day dosing). The sponsor submitted an analysis that concluded that there was a nominally significant (p=0.026) relationship between trough serum concentration and evening diastolic BP (this analysis was not confirmed by our reviewers, who had substantial concerns about the adequacy of the data from study 3003). Finally, — had a dose-dependent effect on resting heart rate. Things are not that simple.

First, the clinical reviewers all agree that there was no demonstrated dose-response for blood pressure reduction demonstrated for — (see reviews for details). The effects on
so that does not offer adequate additional support for a dose-response effect of — on hypertension.

: we are not convinced of t of this novel formulation (although I have little doubt that a properly-done trial would be able to demonstrate that property). There are two possibilities for the observed lack of dose-response with regard to BP lowering. The first possibility is that the trial was underpowered or inadequately conducted to detect such an effect. These are impossible to exclude, although the trial in hypertensives (study 3003) enrolled a similar number of patients as other trials that have successfully demonstrated a dose-response effect for other drugs. The second, and I believe more attractive possibility is that the doses of propanolol used in the — are either at or exceed the 'flat' portion of the dose-response curve for propanolol. There is no difference between 120 and 640 mg of propanolol because both are equipotent at reducing BP. In retrospect, the data used to approve and label Inderal LA is inadequate to detect a dose-response curve for BP lowering as well, and how the doses approved were chosen is not apparent at this time. Using the current paradigm of drug dosing, then, the present data support the approval of the 80 and 120 mg doses of — above which no added benefit is likely.

There is an additional issue regarding the timing of the blood pressure measurements; there were no truly 'trough' measures of BP made, with the latest BP measure occurring around 4 hours before the end of the inter-dosing interval (and up to 8 hours before the next rise in the serum concentrations of propanolol, see Dr. Dorantes' review page 35). The issue is how to dose — once or twice per day. The SBA from Inderal LA suggests that there is adequate antihypertensive effect at ≥80 mg dose given once per day. Given the similarity (but not bioequivalence) of — and Inderal LA, this suggests that once per day is adequate dosing.

CHEMISTRY

Drug Substance
The Chemistry reviewer, Dr. Zimmerman, identified no deficiencies in drug substance. The current data will support a shelf life of .

Drug Product
— is designed to release propanolol with a time-lag of approximately 4 hours, using a timed sustained release (TSR) bead, see chemistry review #1, page 25. This bead is formed from immediate release beads containing propanolol (IR beads) coated to form intermediate release beads (IntR beads), which are in turn coated to form the TSR beads. The Chemistry reviewer has identified one remaining issue related to the dissolution specifications for these TSR beads. Since the specifications for the dissolution of the IR beads needed to be changed (due to a lack of previous data using similar beads), this may impact the dissolution specifications of the TSR bead (see review #2, page 19 for details).

Aside from this deficiency, the Chemists have requested some minor changes in the labeling for — (see page 32 for details).

Container/Closure
No deficiencies were identified.

Environmental Assessment
The environmental assessment (Chemistry review #1, page 65) was considered acceptable.

Microbiology
Not Applicable (oral preparation).

cGMP Inspections
The Office of Compliance has given withhold recommendation pending inspection of a new stability testing site.

PRE-CLINICAL PHARMACOLOGY TOXICOLOGY

No pre-clinical pharmacology/ toxicology review was performed or required, as this application was a 505 (b)(2), relying on previously published toxicology and pharmacology data for propanolol.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The Clinical Pharmacologist, Dr. Dorantes, makes several points in her review, of which the following are most relevant to the approvability of this application:

1) Following administration of — there is a delayed release of propanolol of 2-4 hours, as anticipated by the novel coating mechanism used by the sponsor (this can be seen on page 39 of Dr. Dorantes' review). This delay persisted during multiple dose administration of — (see page 35 of the review). The time to maximum reduction in blood pressure was approximately 8 hours following the dose of — (this value does not differ significantly from Inderal LA, see page 36).
2) The formulation exhibits dose-proportionality between 80 and 640 mg doses in healthy subjects (see pages 11 and 29 of her review).
3) The PK profile for propanolol released from the — formulation is similar to Inderal LA at doses (page 39) with the exception of the earlier rise in serum concentrations seen with Inderal LA.
4) There is no evidence of a 'dumping' phenomenon following food, although food does affect the bioavailability of propanolol from — Fed patients take longer to achieve peak serum concentrations (that is, the lag after taking — is longer) by around 1.3 hours. The consequences of this are the need for patients to take their medication consistently with (or without) food (see page 11 for details).
5) While the pharmacokinetics of propanolol in this formulation were extensively evaluated in healthy volunteers in the early trials (which did not systematically collect changes in BP), the clinical trial that examined the effects of — on blood pressure in a hypertensive population (3003) measured far fewer propanolol concentrations (at peak and trough), severely limiting the ability to derive a PK-PD relationship for BP lowering. The sponsor has asserted that a nominally significant relationship between serum concentration of propanolol and reductions in evening diastolic BP was demonstrated (p=0.026); the Agency was unable to confirm this relationship given the small number of samples collected.
6) While the dissolution methods were acceptable, the Office of Clinical Pharmacology and Biopharmaceutics has recommended a change in the dissolution profiling (see page 9 for details).

MEDICAL/STATISTICAL REVIEW

Antihypertensive Efficacy

The two reviewers of the clinical data (Drs. Karkowsky and Gordon) concluded that — has demonstrated antihypertensive efficacy when compared with placebo for the doses used in the trial (80, 120, 160, and 640 mg of —). Describing the antihypertensive effect, which requires understanding the dose-response relationship and the appropriate dosing interval, however, is another thing and requires additional discussion. I will begin by dismissing any interest in the results of the antihypertensive effects seen at peak serum concentration (*i.e.*, the morning BP measurements). For approval, the issue is assuring that antihypertensive efficacy persists to the end of the inter-dosing interval using the dosing schedule studied.

Dose-Response Relationship

There is, simply put, no evidence of a dose-response for reduction of evening BP for doses of — ≥120 mg (see section 2.3.4 of Dr. Gordon's second review). For doses 80, 120, 160 and 640 mg the placebo-subtracted reductions in mean evening seated DBP were 3.5, 5.6, 3.4, and 4.5 mmHg respectively. A similar lack of dose-response is also seen when the changes in BP in the am, and when systolic BP changes are examined. When asked to provide their rationale for believing a dose-response has been demonstrated, the sponsor pointed to the dose-related decreases in resting pulse rate that were seen in hypertensive patients (see table 14 of their 8.23.2002 submission for an example). This is not evidence of an effect on blood pressure, and an effect on resting heart rate has not even been taken as evidence of an effect on adrenergic tone. When the standard test (exercise heart rate) was performed in healthy volunteers in study 3000, once again there was no dose-dependent effects for doses between 80 and 640 mg of — demonstrated (see Dr. Gordon's initial review, table 6). For doses 80, 120, 160 and 640 mg the mean changes in exercise-induced heart rate at hour 24 were –2.1, -0.2, -0.5, and +4.7 BPM respectively.

Dosing Interval

Dr. Karkowsky has discussed with some elegance the difficulty of understanding the appropriate dosing interval for —. He correctly points out that there are no true 'trough' readings in this development program useful to gauge the antihypertensive effects of — at the inter-dosing interval. What data there are from study 3003, that captures the BP approximately 4 hours before true trough (the 8 hours referred to by Dr. Karkowsky refers to the time from the time of the measurement through the end of the trough period (which adds an additional 4 hours). Dr. Karkowsky is also correct, I believe, in raising the possibility that if Inderal LA is known to have antihypertensive efficacy persisting through throughout 24 hours (where the trough values are similar to those seen with — the it would be possible to make inferences about the persistence of the antihypertensive effect of — through the end of 24 hours, even in the absence of direct measurements of BP beyond 20 hours after dosing. Three things buttress such a course:

1) Dr. Dorantes' conclusions regarding the similarity of the pharmacokinetic profiles of the two drugs during period after Cmax. Both drugs achieve a Cmax and then decline to a trough value that is quite similar (for the 160 mg dose, with dose-proportionality demonstrated for the lower doses), with the significant difference being the duration of the trough level (1 hour for Inderal LA, 4-5 hours for —).
2) The labeled efficacy of Inderal LA through the inter-dosing interval, which indicates BP lowering effects through trough for once a day dosing of 80 mg of Inderal LA. Additional supportive data could come from studies using the lowest dose strength of Inderal LA (60 mg) to provide additional assurance that there is antihypertensive efficacy for the 80 mg — during the 4-8 hours of trough propanolol levels (see Dr. Karkowsky's review page 4). In reviewing the Summary Basis of Approval, the antihypertensive efficacy of Inderal LA 60 mg was apparently evaluated in published double-blind trial comparing Inderal LA 60 mg with propanolol 20 mg TID[1]. While the reprint is not available to me, it apparently found 'indistinguishable' difference in BP lowering for the two formulations. As for the antihypertensive effects of the 80 mg dose of Inderal LA, it was shown to be effective in lowering systolic blood pressure in a trial comparing Inderal LA 80 mg with propanolol 20 mg QID. It is also asserted that there is dose-proportionality for over the range of Inderal LA doses studied. The results of these studies are reflected in the Inderal LA label, which indicates 80 mg is a recommended starting dose.
3) The large amount of information we have about the efficacy of propanolol as an antihypertensive (it is one, after all). While this does not provide data to counter negative findings about this particular formulation (*e.g.*, absence of a dose-response for the doses of — ≥120 mg), or address concerns about the appropriate dosing of this extended release product, propranolol is not 'an unfamiliar substance' as Dr. Temple put it in his approval of Inderal LA.

Where does this leave the issue of determining the inter-dosing interval for —? Based on the line of reasoning put forward above, I am convinced that the pharmacokinetics of propanolol, administered as — are sufficiently similar to those of propanolol administered as Inderal LA in the period following Cmax, and the evidence for a trough effect of Inderal LA 80 mg is sufficiently demonstrated, that — is established as a once per day drug. What is clear, however, is that the precise magnitude of the antihypertensive effect at trough for — cannot be estimated without better data collected at the inter-dosing interval.

[1] Oshima K., Ikeda,M., Goto Y. et al. A study of the hypotensive effect of long-acting propanolol (Inderal LA) on the diurnal variation of blood pressure in essential hypertension. Igaku-no-Ayumi (1983) 330-358.

Special Populations

The statistical reviewer, Dr. Wang, has summarized the BP effects of — in the relevant demographic populations. For the patients grouped by age (<, >65) or gender, there is no evidence of a qualitatively different effect for ' — (see section 4.4 of his review) in any of the subgroups. An unusual analysis of interest (table 11) was conducted: antihypertensive efficacy relative to duration of hypertension, which also found no differences among those with recently-diagnosed hypertension (<1 year) up to those with hypertension for ≥5 years.

Safety

Dr. Gordon reviewed the safety, and the reader is referred there for details. There were no identified surprises for this formulation of propanolol. The highest dose (640 mg) was not well tolerated and its use resulted in discontinuation in a higher percentage of patients (11.5%) than other doses of — (see Dr. Gordon's second review, table 36). Insomnia and fatigue were prominent in the reasons given for discontinuations in the 640 mg dose group.

SUMMARY

— has adequately, if just barely, been characterized as a once per day antihypertensive with effects that peak at doses between 80 and 120 mg. During the extended trough period there is (again just barely) enough data to demonstrate persistence of antihypertensive effect for the 80 and 120 mg doses of — The labeling should reflect this antihypertensive efficacy but remain silent on — as the sponsor did not successfully demonstrate

... The Dosage and Administration section needs to emphasize the importance of taking the drug at a consistent relationship to meals, given the significant food effect seen. The label should also not reflect any information about the blood pressure lowering effects of — during the morning period, as this would falsely imply that there are information available supporting this effect as clinically relevant. The concerns of the Clinical Pharmacologist (changes in dissolution specifications) the chemists (labeling) and DMETS (labeling) should be transmitted to the sponsor for their consideration in the Approvable letter.

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/s/

Doug Throckmorton
8/30/02 03:40:57 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 8, 2002

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader Division of Cardio-Renal Drug, Products HFD-110

TO: Dr. Douglas Throckmorton, Director, Division of Cardio-Renal Drug, Products HFD-110

Subject: Non-approval of NDA 21-438 — Extended Release Propranolol Hydrochloride Capsules (— for the treatment of hypertension —

This memo outlines my rationale for recommending that — Extended release propranolol capsules , — , not be approved for the treatment of hypertension — — under section 505 (b)(2) of the Food, Drug and Cosmetic Act. I have taken an empirical and conservative approach in making this non-approval recommendation for the treatment of hypertension. The only submitted study for the treatment of hypertension is inadequate to conclude that the — affords blood pressure control during the entire dosing interval.

There are two reasons that I chose the empirical approach for this non-approval recommendation. The first is that I believe an approval recommendation sets a poor precedent for other drugs, engineered to deliver drug only after long lag. Secondly, labeling of — would of necessity rely on non-trough blood pressure effects since no "true" trough measurements are available. Neither of these objections, however, is so overwhelming.

It may not be unreasonable to take a more experiential approach, relying on the performance of other sustained release propranolol formulations to fill in the information, not available from the — studies. Should you decide to approve — the flat dose response curve from the single hypertensive study would imply only the 80-mg dose should be approved.

There are still outstanding chemistry issues. Inspection of the site that performed the stability testing is still pending. The recommended expiry dates are still in the process of negotiation between the Agency's chemist and biopharmaceutists and the sponsor. The specifics of the commercial box are also still being worked out since all dose strengths would be identically color coded (not an issue if only the 80-mg dose is approved). Aside from the successful audit of the stability sites none of the other chemistry issues are approvability issues.

DMETS had no objection to the proposed name — No DSI audits were requested, none were, therefore performed. Since I have not recommended approval for either indication, no labeling recommendations are made. Since — is an extended release formulation no pediatric studies are necessary.

With respect to this formulation, — capsules are formulated from microspheres, with the various dosing strengths derived by encapsulating different amounts of these microspheres. Structurally, each of the microspheres consists of two concentric outer coatings, which surround a — propranolol active-drug layer. The — propanolol retards and, therefore, extends the release of propranolol. The first outer coating delays release of active drug for approximately 3 hours. The second coat allows the sustained release of propranolol hydrochloride core over 12 to -16 hour time frame.

The division of Biopharmaceutics (Dr. Angelica Dorantes) reviewed the performance characteristics of this formulation. When — was administered fasting, there is a lag time of approximately 3 hours (the T_{lag} is estimated at 1-hour and reflects the time till drug is first measurable, but the concentration versus time curve inflects upward at approximately 3-4 hours). The concentration of propranolol then rises to reach T_{max} at approximately 12 hours. The terminal half-life is approximately 8.4 hours. Over the dose range of 80-640 mg daily, both C_{max} and $AUC_{0-\infty}$ are approximately dose proportional. A high fat meal alters the release characteristics of this formulation with a prolonged time till the concentrations inflect upward (to 5 hours) and a delayed T_{max} (to 15 hours) and an approximately 20% increase in AUC (90% CI 106-133%). Variability of performance appears reasonable with an approximately 35-40% coefficient of variation in C_{max} and a 50% coefficient of variation in exposure (AUC).

Blood Pressure:

A single clinical 8-week trial that randomized 434 subjects with mild-moderate hypertension was submitted to support the approval of — -extended propranolol hydrochloride formulation for the treatment of hypertension. Subjects were divided in a 1: 1: 1: 1: 1 ratio to receive either placebo or — at a dose of either 80, 120, 160 or 640 mg daily. — was taken between 9:30 and 10:30 PM, with no limitation as to food intake. Pivotal vital sign measurements for the study were scheduled during the morning hours between 6:00 to 10:00 AM (the AM measurement). Additional blood pressure measurements were scheduled for 5:30-6:30 PM (the PM measurement).

The results of the study are shown in Table 1.

Table 1. Analysis of Covariance* of blood pressure and heart rate at AM and PM

		Sitting PM Measurements			Sitting AM measurements		
		Diastolic BP	Systolic BP	Heart Rate	Diastolic BP	Systolic BP	Heart Rate
	Placebo	N=75 -7.8 Δ= NA	N=75 -7.6 Δ= NA	N=75 -3.5 Δ=NA	N=84 -7.0 Δ=NA	N=84 -8.2 Δ=NA	N=84 -2.0 Δ=NA
	80	N=79 -11.4 Δ= -3.6	N=79 -14.0 Δ= -6.4	N=79 -6.7 Δ= -3.2	N=88 -10.1 Δ=-4.1	N=88 -12.0 Δ=-3.8	N=88 -6.1 Δ=-4.1
	120	N=78 -13.3 Δ=-5.5	N=78 -13.0 Δ= -5.4	N=78 -8.3 Δ= -5.8	N=84 -11.0 Δ= -4.0	N=84 -12.4 Δ= -4.2	N=84 -7.0 Δ= -5.0
	160	N=82 -11.4 Δ=-3.6	N=82 -11.3 Δ= -3.7	N=82 -10.3 Δ= -6.5	N=84 -10.4 Δ= -3.4	N=84 -12.2 Δ=-4.0	N=84 -8.8 Δ= -6.8
	640	N=80 -12.2 Δ= -4.4	N=80 -13.5 Δ= -5.9	N=80 -11.3 Δ= -7.8	N=87 -10.7 Δ= -3.7	N=87 -12.1 Δ= -3.9	N=87 -10.4 Δ=-8.4
	p-value	0.001	0.046	0.000	0.018	0.345	0.000

*Covariates are treatment, center and baseline

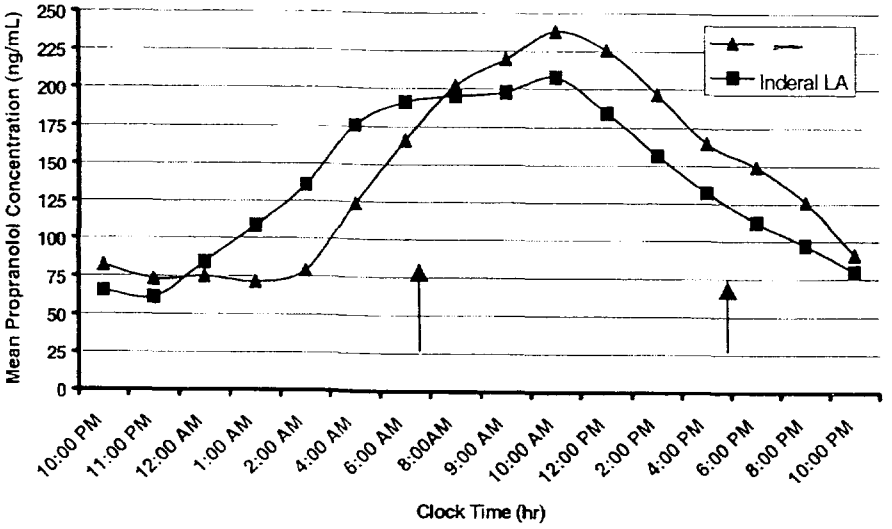
— adequately controls blood pressure both at the AM and PM measurements. There was no dose relationship to the magnitude of effect. Heart rate changes are similar between the AM and PM measurements but the decrease in heart rate is clearly dose-related.

The study, however, did not establish a blood pressure effect during the entire 24-hour dosing interval. Dosing was timed to 9:30 to 10: 30 PM. Measurements of vital signs were scheduled from between 5:30 and 6:30 PM for the "trough" or PM measurement, and between 6:00 to 10:00 AM for the "peak " or AM measurements. The PM measurements capture the blood pressure effect approximately 8 hours prior to the true drug trough measurements.

To put the timing of the measurements in perspective, I've reproduced the serum concentration versus time effect of — compared to Inderal LA both at 160 mg after chronic dosing (study 3006; graph taken from Dr. Dorantes review). The drug was administered fasting. The concentrations of — after a meal would shift by approximately an additional 2 hours the time to trough concentration.

Trough — concentration occurs somewhere 1 and 2 AM and are approximately 70-75 ng/ml in this study. The timing of the measurements at 6-10 AM and 5:30-6:30 PM would be obtained when serum concentration of — is approximately 150-200 ng/ml (arrows). It is clear that the timing of the measurements did not capture the trough propranolol concentrations.

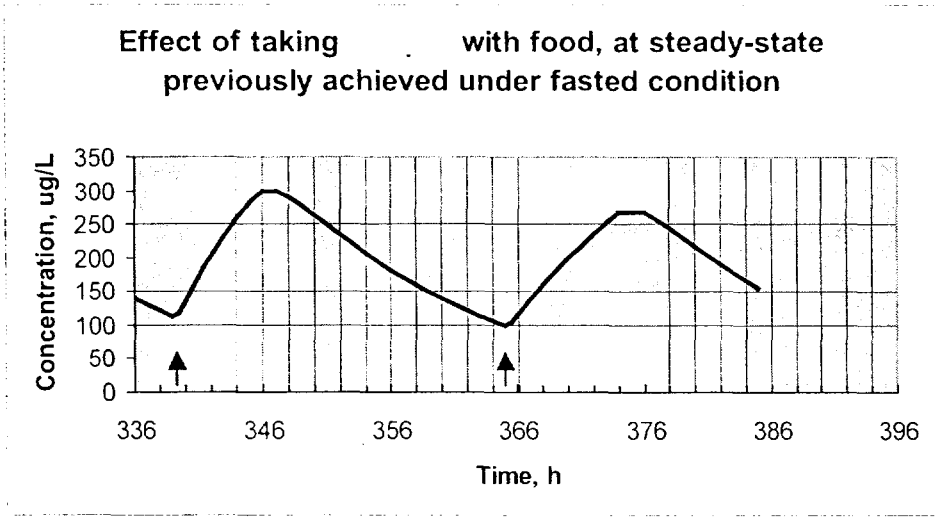
Figure 1. Kinetic time course of — and Inderal LA at 160 mg daily.



Any reliance on the concentration-effect relationship of Inderal LA to support the approval of — would have to assume that other differences in the kinetic performance of Inderal LA would be irrelevant to imputing a "trough" effect for — . First, the duration for which — hovers around its nadir concentrations is approximately 4 hours (from 10PM to 2AM), the equivalent time for Inderal LA is only one hour (at the interdosing interval). One would, therefore, have to assume that the duration at trough concentrations have no effect on trough blood pressure effect (an assumption that hysteresis is negligible).

Food effects also should be considered in imputing any trough effect of — relative to Inderal LA. Dr. Gobburu simulated the steady state concentrations of propranolol, with all doses of — taken fasting with the exception of the last dose that was taken after a high fat meal (Figure 2). The data was synthesized by the supperposition of the single dose data. The consequence of a fatty meal is to increase the lag time by an additional 2-3 hours with the attendant continued elimination of propranolol before input from the index dose becomes evident. Under these circumstances the concentrations of — would likely be 20% lower than the same concentrations after the ingestion of — fasting and also 20 % lower than the corresponding Inderal LA concentrations. If it is assumed that the dose range which was studied is on the flatted portion of the dose-response curve, the difference in concentrations could well be discounted.

Figure 2.



In summary, approval of — for use in hypertension would of necessity rely on the measured 16- hour blood pressure effect with this formulation as well as the imputed values of blood pressure at trough. The imputed values assumed to be equivalent to the effect of Inderal LA based on nearly equivalent trough measurements. The approval would also need to assume that the differences of kinetic performance between — and Inderal LA are irrelevant to estimating the imputed trough blood pressure effects.

Safety:

There are no unusual safety issues. Given the small controlled database no unanticipated or unexplained adverse events occurred with — treatment.

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/s/

Abraham Karkowsky
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MEDICAL OFFICER

Phase I Safety evaluation for —
NDA#21,438
Drug Name: — (propranolol hydrochloride)
Sponsor: Reliant Pharmaceuticals
Medical Reviewer: Maryann Gordon, M.D.

Conclusion

There were 5 studies conducted with healthy volunteers: 2 studies compared the pharmacokinetics of — to that of Inderal®LA, 1 was a food effect study, 1 was a dose proportionality study, and 1 compared the pharmacokinetics of — 80 mg and 160 mg. All but one study used single doses of study drug, and the dose range was 80 mg to 160 mg. There were no reported deaths or serious adverse events. These studies are briefly discussed below. None suggests a safety concern that is different from what one expects with propranolol.

Study 3000: this was a randomized, 2 period crossover, double blind pilot trial evaluating the safety and pharmacokinetics of single dose — 80 mg and 160 mg in 12 healthy male volunteers.

AUC and Cmax for both doses are shown in the table below.

[redacted] Reliant Pharmaceuticals LLC)
3000 [redacted]
Clinical/Statistical Report

Page 1 of 1
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Post-Text Table 14.1.9
Summary of Analysis of Variance on Pharmacokinetic Parameters
Bioavailability Population

Parameter/Statistic (a)		[redacted] 80 mg (N = 12)	[redacted]160 mg (N = 12)	Ratio (160mg/80mg) (N = 12)
AUC (0-72 hrs) (ng-hr/mL)	N	12	12	12
	Adjusted Mean	1894.5	4203.7	2.2
	90% CI	(1761.26, 2037.87)	(3907.97, 4521.74)	(2.00, 2.46)
AUC (0 inf) (ng-hr/mL)	N	12	12	12
	Adjusted Mean	1936.8	4250.4	2.2
	90% CI	(1798.19, 2086.19)	(3966.58, 4578.09)	(1.98, 2.44)
Cmax (ng/mL)	N	12	12	12
	Adjusted Mean	109.0	234.8	2.2
	90% CI	(103.27, 114.98)	(222.52, 247.76)	(2.00, 2.32)

Plasma concentrations for both doses over time are shown in the figure below.

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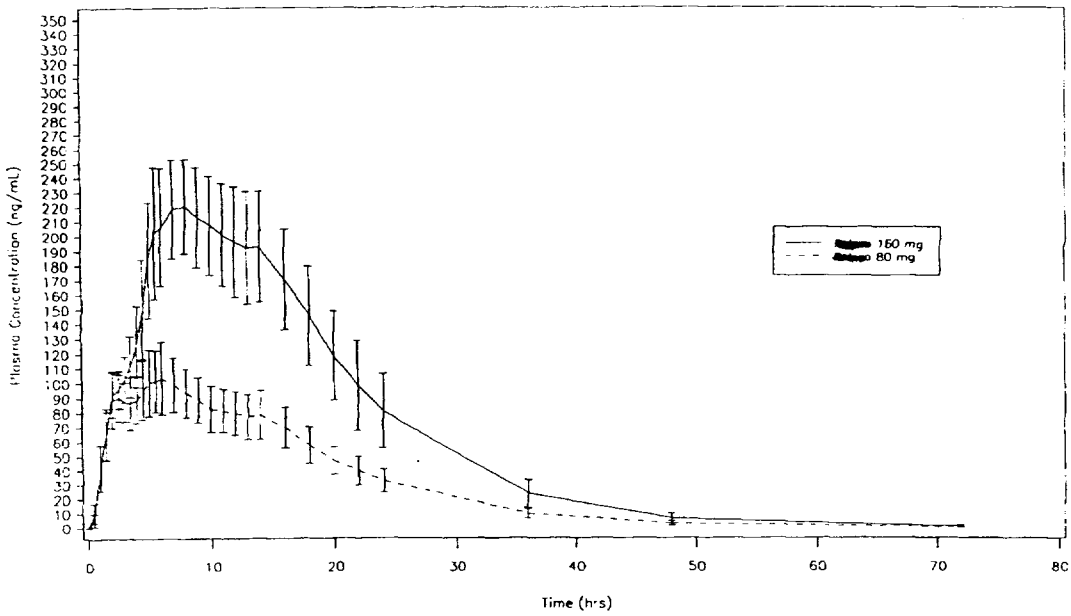
Mean Plasma Total Propranolol Concentration Over Time by Dose

Bioavailability Population



The 12 subjects were all male, mostly black (92%) and had a mean height of 173.4 cm and mean weight of 75.6 kg. All subjects completed the study and no serious adverse events were reported. There were 3 subjects who reported headache: 1 with both doses, 1 with only the 160 mg dose, and 1 with only the 80 mg dose.

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Table 18: Changes in Heart Rate From Pre-dose Over Time - Safety Population

Time / Statistic	Placebo (N=39)	80 mg (N=39)	120 mg (N=39)	160 mg (N=39)
Heart Rate (bpm)				
Hour 2				
N	36	38	36	37
Mean±SD	-3.3±11.46	-4.9±10.40	-5.2±10.29	-5.0±9.51
Hour 4				
N	36	38	36	37
Mean±SD	-0.8±8.21	-1.4±10.10	-2.2±9.03	-2.1±10.78
Hour 8				
N	36	38	36	37
Mean±SD	-7.3±9.0	-7.0±13.02	-9.0±10.74	-8.1±13.01
Hour 10				
N	36	38	36	37
Mean±SD	-4.3±8.26	-7.7±12.91	-8.2±10.95	-7.3±13.53
Hour 12				
N	36	38	36	37
Mean± SD	4.4±7.56	0.2±10.03	-2.1±9.35	-1.5±10.46
Hour 14				
N	36	37	36	37
Mean±SD	1.2±9.71	-5.2±13.03	-2.9±10.94	-2.8±10.28
Hour 18				
N	36	37	36	37
Mean±SD	2.6±7.65	-3.7±12.00	-3.9±11.05	-4.7±12.14
Hour 24				
N	36	37	36	37
Mean±SD	1.3±7.75	-4.1±12.39	-4.8±11.99	-6.2±10.54
Hour72				
N	36	37	36	37
Mean±SD	6.6±8.14	4.3±9.57	5.3±12.24	3.6±10.09

SD = standard deviation
Reference Documentation: Table 14.1.20

Secondary efficacy parameters
Changes in heart rate, rate pressure product and systolic blood pressure at 12 hours are shown below by dose.

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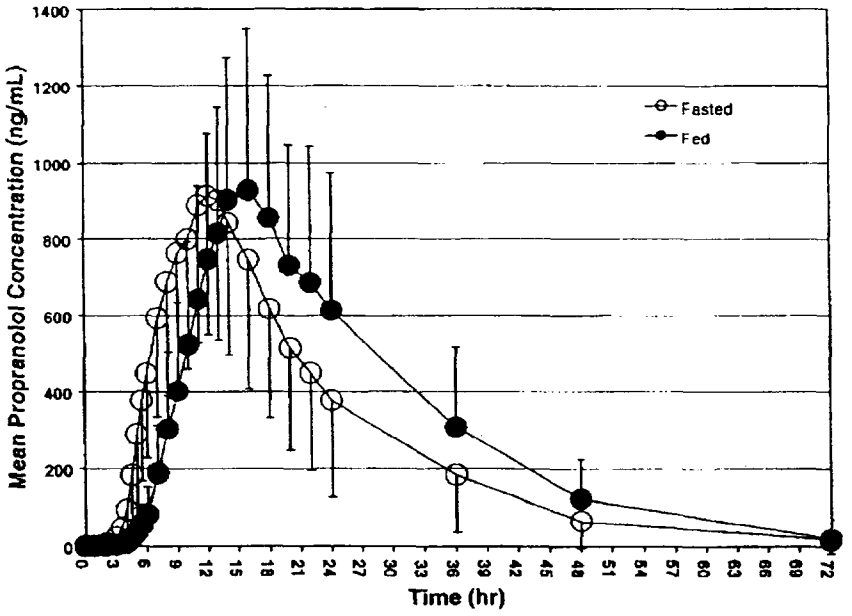
Protocol 3002 was randomized, open-label, two-period cross-over study to assess the effect of food on — bioavailability in healthy adult subjects. The study's objective was to evaluate the effect of concomitant food intake on the bioavailability of — in healthy subjects.

This was a randomized, unblinded, single center, two-period, cross-over trial that evaluated the effect of food on bioavailability after administration of 640 mg of oral — given as four 160mg — capsules. Thirty healthy subjects were randomly assigned to one of two possible sequences. Eighteen subjects were randomly assigned to each sequence. There was a 7-day washout period between doses. Adverse events, vital signs and samples for plasma protocol levels were collected for 72-hr post-dose.

The figure below shows the mean plasma concentration for both fasting and fed states measured over 72 hours.

Figure 1: Mean (± SD) Concentration-Time Profile of a Single 640 mg Dose of —



There was delayed Tmax in the fed state (15.4 hr vs. 11.5 hr) and somewhat higher AUC (18975 ng*hr/ml vs. 22178 ng*hr/ml).

Safety
There were no reports of death or serious adverse events. Two subjects discontinued prior to the second dosing phase (1 withdrew for nausea and vomiting during the first phase and one withdrew consent after the first phase).

Protocol 3006: a single and multiple dose, two-period, cross-over study to evaluate the bioavailability and safety of — 160mg Relative to Inderal® LA 160mg in healthy, adult male subjects.

Objective: The primary objective of the study was to evaluate the bioavailability and safety of —— 160 mg relative to that of Inderal® LA 160 mg during single dose and multiple dose administration.

This was a randomized, open-label, two-period, cross-over trial evaluating the single and multiple dose bioavailability and safety of oral —— 160 mg capsules relative to Inderal ®LA 160mg capsules in healthy, adult male subjects. Subjects were randomly assigned to one of the two possible sequences of the two treatments. In Period 1 of the study, following a 4-hour fasting period on Day 1, subjects received a single dose of the study drug (—— or Inderal®LA) that they were randomly assigned to receive for the dosing period. Serial blood samples for plasma total propranolol determinations were collected for 72 hours. Subjects received a daily dose of their Period 1 drug on Days 4 to 8. On Days 5 through 8, 24-hour (trough) blood samples were collected for plasma propranolol determinations. After five daily doses of drug, 24-hour serial blood samples were collected for steady state plasma propranolol determinations. A seven-day washout period followed, and the same procedures were followed for Period 2 with the other study drug as determined by the sequence to which the subject was randomized.

Thirty six subjects were randomized and 35 completed the study. First dose mean plasma concentrations for both drug groups are shown below.

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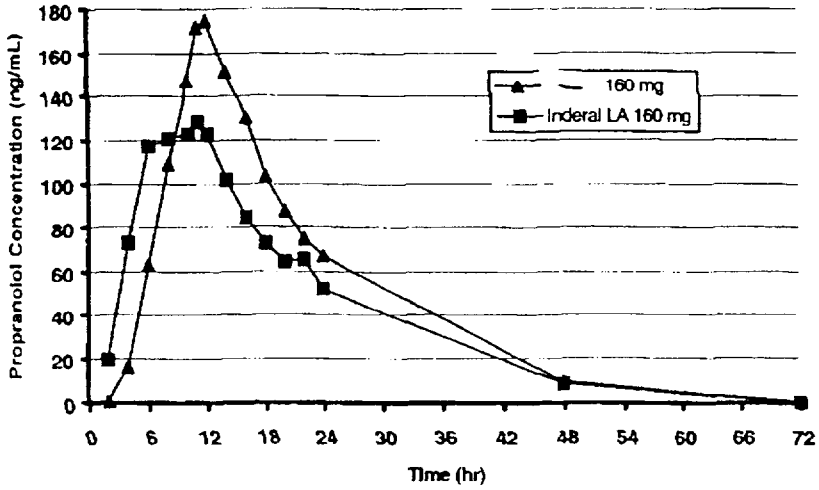
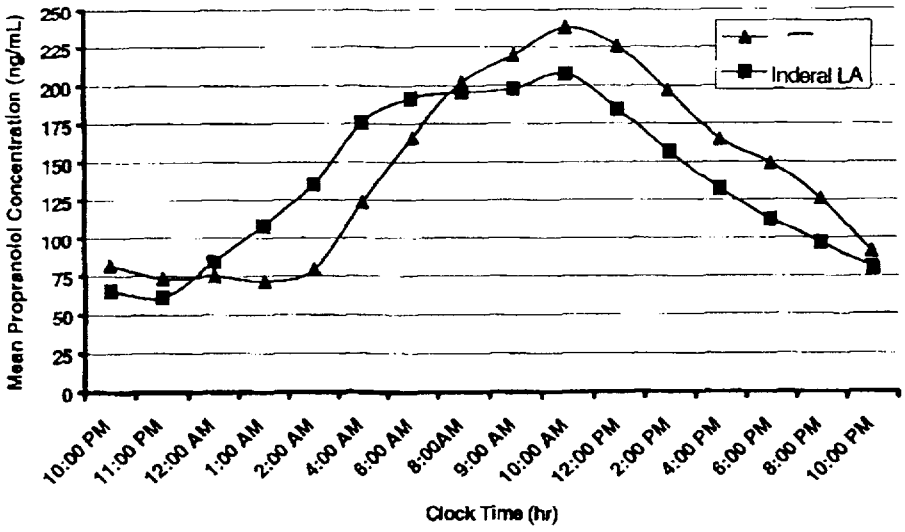
Figure 1: Mean Concentration-Time Profiles of — 160 mg Compared With Inderal® LA 160 mg (Single Dose)



Steady state mean plasma concentrations for both drug groups are shown below.

Figure 2: Mean Concentration-Time Profiles of — 160 mg Compared With Inderal® LA 160 mg (Steady State)



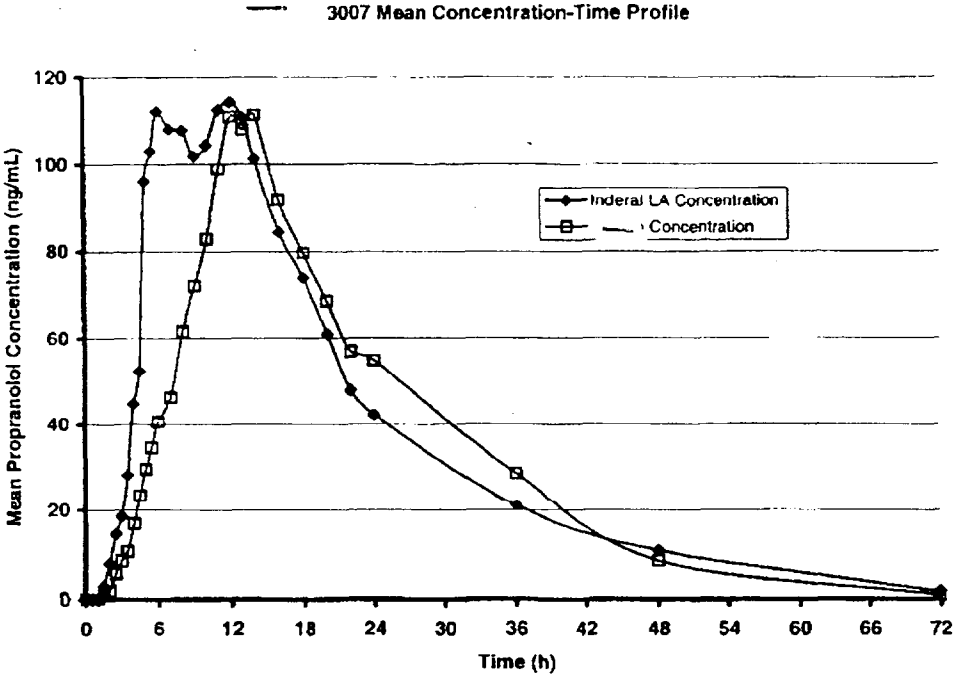
Safety

There were no reports of death or serious adverse events. There was one discontinuation for adverse events. This subject discontinued after reporting dizziness, bradycardia, and fatigue after completing the first dosing phase (— 160 mg).

Protocol 3007: a single dose, two-period, cross-over study to evaluate the safety and preliminary pharmacokinetics of , — 160 mg relative to Inderal LA 160 mg in healthy subjects.

The objectives of this study were to evaluate the preliminary pharmacokinetics and safety of — 160 mg relative to that of Inderal LA 160 mg following single dose administration in healthy male subjects. This was an open-label, randomized, active-controlled, two-period, cross-over trial that evaluated the single dose preliminary pharmacokinetics and safety of oral — 160mg capsules relative to Inderal LA 160 mg capsules. Twelve healthy male subjects were randomly assigned to one of two possible sequences.

The plasma concentrations for the 2 drugs are shown below.



Safety
There were no reported deaths or serious adverse events or discontinuations.

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/s/

Maryann Gordon
8/5/02 06:26:16 AM
MEDICAL OFFICER

MEDICAL REVIEW OF SAFETY AND EFFICACY

NDA#21,438
Drug Name: — (propranolol hydrochloride)
Sponsor: Reliant Pharmaceuticals
Medical Reviewer: Maryann Gordon, M.D.
Date: 5-1-02

Introduction

is a controlled release form of propranolol hydrochloride designed for once a day use.

Conclusions

The one clinical efficacy trial in hypertensive patients (protocol 3003) found that — in doses 80mg to 640 mg taken once daily lowered sitting diastolic and systolic blood pressure compared to placebo. There was a small dose response for blood pressure lowering effects and a more prominent one for heart rate lowering effects.

More patients randomized to — 640 mg discontinued treatment for an adverse event compared to the other dose groups. Also, there was a slightly higher reporting incidence of all adverse events with the 640 mg — dose compared to the lower doses. Events reported by more than 2% of the patients who received — (all doses combined) and more often than in the placebo group include fatigue and dizziness (excluding vertigo).

Financial disclosure

Reviewed by medical reviewer

1.0 Efficacy

1.1 Study Design: randomized, double blind, parallel, placebo controlled with 5 treatment arms. The study duration was 10 weeks.

1.2 Study Objective: efficacy of — treatment compared to placebo in lowering diastolic blood pressure.

1.3. Patient Type: patients with essential hypertension

1.3.1. Inclusion Criteria: subjects who were

-male or female;
-18 years or older;
-female subjects who were either post-menopausal for 2 years, surgically sterile, or using effective methods of contraception (intrauterine device, oral contraceptives); female subjects who were to have a negative serum human chorionic gonadotropin for pregnancy at study entry;
-had a clinical diagnosis of essential hypertension, either newly diagnosed or previously treated;
-were outpatients;
-agreed not to make changes to dietary, exercise, or smoking habits and were not to enter a weight loss program during participation in the study after signing the informed consent form.

At randomization, mean sitting diastolic blood pressure had to be between 96 mmHg and 114 mmHg (inclusive) at 2 consecutive visits (at randomization and 1 week prior to randomization) and mean sitting systolic blood pressure had to be <200 mmHg at 2 consecutive visits (at randomization and 1 week prior to randomization).

1.3.2 Exclusion Criteria Subjects excluded were those who:
were pregnant or nursing; had abnormal physical or laboratory findings or a medical condition which would place the subject at risk or interfere with the subject's ability to participate in the study; were suspected of having renal artery stenosis (presence of abdominal bruits combined with drug-resistant hypertension or recent acceleration of hypertension); had any disease of the gastrointestinal system, liver, or kidneys, or any condition which compromises the function of these systems and could result in the possibility of altered absorption, excess accumulation, or impairment of metabolism or excretion of the study drug or its metabolites; were to have discontinued all antihypertensive medications prior to entering the study (subjects were not asked to discontinue their existing antihypertensive treatment and other excluded medications before informed consent had been obtained for this study; Visit S1 related procedures were performed after the subject discontinued antihypertensive and/or excluded medications); suffered from significant cardiac disease such as myocardial infarction, unstable angina, stroke, clinically significant bradycardia (<50 beats/minute), or greater than first degree A-V block during the 6 months preceding study entry; had clinically relevant cardiac valvular disease (e.g., aortic or mitral stenosis, aortic or mitral insufficiency); had congestive heart failure (CHF) (except Class I CHF not requiring therapy); had major surgery, including coronary artery bypass graft (CABG), during the 6 months preceding study entry; had a history of malignancy including leukemia and lymphoma (but not basal cell skin cancer) within the last 5 years; had a current history of asthma, chronic obstructive pulmonary disease (COPD), or nonallergic bronchospasm (e.g., chronic bronchitis, emphysema) requiring treatment; had insulin-dependent diabetes mellitus or had a history of hypoglycemia; had a history of drug abuse or recent (within the last 12 months) history of excessive alcohol consumption defined as >2 drinks/day (>3 oz of 80 proof alcohol or equivalent); had any condition that the investigator believed might affect the subject's safety or impact the accuracy of study data; had a language barrier or any other problems precluding good communication or cooperation; had a hypersensitivity to propranolol or any of its components; participated (except screened but failed to participate) in any investigational clinical trial within the last 30 days; were unable to give informed consent; had previously enrolled in a — study; had concomitant administration of agents known to affect blood pressure or agents known to affect the activity of propranolol, including antidepressants (excluding SSRIs), phenothiazides, bronchodilators, peripheral vasodilators, were currently being treated with an ophthalmic preparation containing beta-adrenergic antagonists.

1.4 Sample Size: planned sample size was 420 subjects.

1.5 Dose and duration: the 5 treatment arms were once daily placebo, — 80 mg, — 120 mg, — 160 mg, and — 640 mg. The total study duration was 10 weeks with 2 week run-in, 6 weeks of double blind treatment, and 2 weeks of down titration. Patients were instructed to take study medication between 9:30 and 10:30 PM. Clinic visits were scheduled between 6 and 10 AM.

Figure 1: Schematic Design Diagram

Period	Placebo Run-in Phase				Treatment Phase				End of Down Titration
Week	Screen	1	2		0	2	4	8	10
Visit	S1	S2	S3		R1	R2	R3	R4	R5
					AM	AM	AM	AM	AM
					PM		PM	PM	

The treatment schedule is shown below

Table 1: Treatment Schedule

	Placebo Run-in Phase	Treatment Phase				
Treatment Group		Up Titration		Stable	Down Titration	
	-2 or -3 Weeks	Week 1	Week 2	Weeks 3 to 8	Weeks 9 and 10	
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
80 mg	Placebo	80 mg	80 mg	80 mg	80 mg	80 mg
120 mg	Placebo	80 mg	80 mg	120 mg	80 mg	80 mg
160 mg	Placebo	80 mg	80 mg	160 mg	80 mg	80 mg
640 mg	Placebo	160 mg	320 mg	640 mg	320 mg	160 mg

Note: Treatment weeks are inclusive (ie, Week 1 includes all study treatment received from randomization through the end of the first week of treatment).

1.6 Study Procedure: the schedule of events and evaluations required by the protocol is shown below.

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Table 3: Schedule of Assessments

Period	Placebo Run-In Phase			Double-blind Treatment Phase							End of Down Titration
Week[a]	Screen	1[b]	2	0		2	4		8		10
Visit[a]	S1	S2	S3	R1 AM	R1 PM	R2 AM	R3 AM	R3 PM	R4 AM	R4 PM	R5
Medical History	X										
Physical Examination	X								X		X
Trough Vital Signs (5:30–6:30 PM)					X			X		X	
Morning Vital Signs(6-10 AM)	X	X	X	X		X	X		X		X
Randomization					X						
12-Lead ECG	X										X
Laboratory Assessments	X										X
Blood draw for plasma propranolol levels[c]								X		X	
Adverse Experiences		X	X	X		X	X		X		X
Concomitant Medications	X	X	X	X		X	X		X		X
Dispense Study Medication	X	X	X		X	X		X		X	
Collect/Count Study Medication		X	X	X		X	X		X		X
Randomized Treatment Completion									X		
Termination											X

[a] Week and Visit numbers refer to assessments on the first day of a treatment week.
[b] At week 1 of run-in phase (S2) visit, if subject did not meet randomization criteria for blood pressure, the single blind run-in period was extended for one more week, and the subject was scheduled for Visit S3.
[c] Blood draw for plasma propranolol levels were collected for subjects included in the Pharmacokinetic subgroup study only.

1.7 Protocol defined study primary efficacy variable: mean change from baseline[1] to week 8 in sitting (morning) diastolic blood pressure. Patients were instructed to take their study drug in the evening. Trough[2] blood pressure measurements were recorded at baseline and visits 4 and 8.

1.8 Secondary endpoints: change from baseline to week 8 for mean sitting systolic blood pressure, pulse rate, and mean sitting blood pressure-rate product[3] measured in the morning and evening, and mean sitting diastolic blood pressure measured in the evening.

1.9 Disallowed concomitant medications: other antihypertensive medications as well as bronchodilators, antipsychotics, phenergan, and antidepressants.

1.10 Protocol amendments: minor changes to protocol were made on 3-12-01. A summary of the changes is listed below:

[1] Baseline is defined as the latest measurement obtained just before randomization
[2] 24 hr after dosing
[3] mean sitting systolic blood pressure multiplied by the pulse rate

The purpose of this amendment is to revise sections of Protocol 3003 [redacted] to modify and clarify the exclusion criteria, the evaluations performed when patients prematurely discontinue from the study, the schedule of ECG and clinical laboratory assessments, the efficacy and pharmacokinetic parameters, the procedure for emergency unblinding, and concomitant medications allowed during the study.

Patients will not be asked to discontinue their existing antihypertensive treatment or other excluded medications before informed consent has been obtained for this study. All medications prohibited by the protocol must be discontinued prior to the performance of screening procedures at Visit S1.

If patients are prematurely withdrawn from the study on or before Day 7 of the double-blind treatment period, Visit R5 study termination evaluations will be made. If patients prematurely discontinue from the study after Day 7 of the double-blind treatment period, Visit R4 procedures will be completed; and Visit R5 evaluations will be made within the following 2 weeks. Patients who experience significant orthostatic symptoms together with a clinically significant orthostatic decrease in BP will be withdrawn from study medication and discontinued from the study; Visit R5 evaluations will be made.

Clinical laboratory tests and 12-lead ECGs will be performed at Visit R5 instead of Visit R4.

Primary and secondary efficacy parameters will be measured as changes from baseline to Week 8. Pharmacokinetic analyses will be performed in a subgroup of patients.

The procedure for the emergency unblinding of study medication has been changed because code break envelopes and/or pouches will not be supplied to the study site. Instead, emergency code break information will be supplied on the drug label attached to each drug kit.

Selective serotonin re-uptake inhibitors (SSRIs) will be allowed as concomitant medications if patients are already receiving a stable dose prior to participation in the study.

2.0 Results

2.1 Patient disposition: 680 subjects were screened; 434 of these were randomized at 41 sites. The numbers of subjects per treatment group ranged from 85 to 89. Patients who discontinued prematurely from the trial by reason are shown below, by treatment group.

Number and (percent) of patients

	Placebo N=88	— 80 mg N=89	— 120mg N=85	— 160mg N=85	— 640mg N=87
No. completed	66 (75)	73 (82)	72 (85)	73 (86)	72 (83)
No. discontinued	22 (25)	16 (18)	13 (15)	12 (14)	15 (17)
No. with no post baseline data	4	1	1	1	0
Reason for discontinuation+					
Adverse event	5	6	3	1	9
Lack of effect	6	2	2	2	0
Lost to follow up	6	3	1	1	0
Withdrew consent	2	2	5	2	2
Protocol violation	1	0	0	0	0
Other=	2	3	2	6	4

+There could be more than 1 reason for discontinuation
#includes noncompliant with study visits (9), non compliance (4), missed R4-V8 (2), increased blood pressure (2).

Overall, the drop outs were similar between the groups. The discontinuation rate was slightly higher for the placebo group (25%) than for the active treatment groups (14-18%). There were 7 patients with no post baseline data (4 placebo and 1 each for the 3 — groups). The group who received — 640 mg had the highest rate of discontinuation for an adverse event (10%) while the placebo group had the highest rate of discontinuation for lack of effect (7%).

2.2 Patient demographics and baseline characteristics: are shown in the following 2 tables.

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Table 7: Demographic Characteristics - Intent-to-Treat Population

Parameter	Placebo N = 84	80 mg N = 88	120 mg N = 84	160 mg N = 84	640 mg N = 87	P-value[a]
Age (years)						
N	84	88	84	84	87	0.566
Mean ± SD	54.3 ± 10.48	55.1 ± 10.90	53.4 ± 10.61	55.0 ± 10.74	56.1 ± 11.07	
Age (n, %)						
18-24	1 (1.2)	0	0	0	0	NA
25-29	1 (1.2)	2 (2.3)	1 (1.2)	1 (1.2)	0	
30-49	24 (28.6)	27 (30.7)	32 (38.1)	24 (28.6)	25 (28.7)	
50-64	48 (57.1)	41 (46.6)	40 (47.6)	41 (48.8)	43 (49.4)	
≥65	10 (11.9)	18 (20.5)	11 (13.1)	18 (21.4)	19 (21.8)	
Gender (n, %)						
Male	48 (57.1)	50 (56.8)	46 (54.8)	51 (60.7)	48 (55.2)	0.958
Female	36 (42.9)	38 (43.2)	38 (45.2)	33 (39.3)	39 (44.8)	
Ethnic Origin (n, %)						
Asian	0	1 (1.1)	1 (1.2)	2 (2.4)	0	0.751
Black	12 (14.3)	18 (20.5)	15 (17.9)	12 (14.3)	16 (18.4)	
Caucasian	61 (72.6)	52 (59.1)	54 (64.3)	54 (64.3)	58 (66.7)	
Hispanic	11 (13.1)	16 (18.2)	13 (15.5)	16 (19.0)	12 (13.8)	
Other	0	1 (1.1)	1 (1.2)	0	1 (1.1)	

Most patients were at least 50 years of age, with 12-22% being at least 65 years. The majority of patients were male and white; only 14% to 21% were black. The groups were well balanced.

Table 7 Demographic Characteristics - Intent-to-Treat Population (continued)

Parameter	Placebo N = 84	80 mg N = 88	120 mg N = 84	160 mg N = 84	640 mg N = 87	P-value[a]
Height (inches)						
N	84	88	84	84	87	0.819
Mean ± SD	67.1 ± 4.07	67.0 ± 3.92	66.7 ± 4.21	67.4 ± 3.51	67.1 ± 4.15	
Weight (kilograms)						
N	84	88	84	84	87	0.318
Mean ± SD	88.35 ± 17.158	91.16 ± 18.964	91.52 ± 20.414	91.22 ± 19.428	93.73 ± 21.364	
Duration of Hypertension (years)						
N	82	87	83	83	86	0.353
Mean ± SD	9.1 ± 9.497	8.4 ± 7.840	8.2 ± 7.727	9.0 ± 8.649	10.2 ± 10.526	
Duration of Hypertension (n,%)						
<1 year	8 (9.5)	9 (10.2)	6 (7.1)	4 (4.8)	9 (10.3)	NA
≥1 to 4 years	26 (31.0)	27 (30.7)	26 (31.0)	24 (28.6)	25 (28.7)	
≥5 years	48 (57.1)	51 (58.0)	51 (60.7)	55 (65.5)	52 (59.8)	
Unknown	2 (2.4)	1 (1.1)	1 (1.2)	1 (1.2)	1 (1.1)	

SD = standard deviation, NA = not applicable.
[a] P-value for comparison among treatment groups using Cochran-Mantel-Haenszel general associated statistic adjusted for discrete variables and using ANOVA with factors for treatment and center for continuous variables.
Reference Documentation: Table 14.4.1

The groups were similar for height, weight, and duration of hypertension. Mean duration of hypertension ranged from 8 to 10 years.

2.2.2. Duration on double blind medication

Duration of study treatment for the randomized groups is shown below.

Table 24: Duration of Treatment - Safety Population

	Placebo N=88	80 mg N=89	120 mg N=85	160 mg N=85	640 mg N=87
Duration of Treatment (Days)					
Mean ± SD	64.0 ± 16.70	64.8 ±17.57	66.3 ± 14.38	68.5 ± 9.40	64.9 ± 16.92
Duration of Treatment : N (%)					
Unknown	6 (6.8)	2 (2.2)	2 (2.4)	2 (2.4)	0
Day 1-14	2 (2.3)	6 (6.7)	2 (2.4)	1 (1.2)	3 (3.4)
Day 15-28	4 (4.5)	1 (1.1)	2 (2.4)	0	5 (5.7)
Day 29-42	5 (5.7)	1 (1.1)	2 (2.4)	2 (2.4)	2 (2.3)
Day 43-56	3 (3.4)	2 (2.2)	4 (4.7)	2 (2.4)	1 (1.1)
Day 57-70	45 (51.1)	54 (60.7)	49 (57.6)	48 (56.5)	50 (57.5)
Day >70	23 (26.1)	23 (25.8)	24 (28.2)	30 (35.3)	26 (29.9)

SD = standard deviation.
Reference Documentation: Table 14.9

Mean duration of treatment was similar across the groups. Most patients received treatment for $\geq$ 57 days.

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2.2.3 Concomitant diseases

Summary of previous and concomitant diseases is shown below.

Table 9: Relevant Medical History and Concurrent Disease - Safety Population

Condition/Disease[a]	Placebo N = 88	80 mg N = 89	120 mg N = 85	160 mg N = 85	640 mg N = 87	Total N = 346
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects With At Least One Reported	88 (100)	89 (100)	85 (100)	85 (100)	87 (100)	346 (100)
Hypertension[b]	88 (100)	89 (100)	85 (100)	85 (100)	87 (100)	346 (100)
Drug Hypersensitivity	14 (15.9)	16 (18.0)	19 (22.4)	19 (22.4)	7 (8.0)	61 (17.6)
Dyspepsia	9 (10.2)	10 (11.2)	9 (10.6)	10 (11.8)	15 (17.2)	44 (12.7)
Hypercholesterolemia[c]	19 (21.6)	18 (20.2)	11 (12.9)	10 (11.8)	16 (18.4)	55 (15.9)
Hyperlipidemia NOS[c]	8 (9.1)	9 (10.1)	13 (15.3)	8 (9.4)	11 (12.6)	41 (11.8)
NIDDM	8 (9.1)	12 (13.5)	7 (8.2)	6 (7.1)	11 (12.6)	36 (10.4)
Hysterectomy NOS	11 (12.5)	10 (11.2)	8 (9.4)	4 (4.7)	13 (14.9)	35 (10.1)
Back Pain	3 (3.4)	8 (9.0)	11 (12.9)	7 (8.2)	7 (8.0)	33 (9.5)
Menopause[d]	10 (11.4)	8 (9.0)	9 (10.6)	9 (10.6)	6 (6.9)	32 (9.2)
GERD	5 (5.7)	6 (6.7)	10 (11.8)	7 (8.2)	8 (9.2)	31 (9.0)
Myopia	9 (10.2)	7 (7.9)	8 (9.4)	8 (9.4)	8 (9.2)	31 (9.0)
Depression NEC	6 (6.8)	8 (9.0)	3 (3.5)	8 (9.4)	9 (10.3)	28 (8.1)
Headache NOS	10 (11.4)	5 (5.6)	8 (9.4)	8 (9.4)	6 (6.9)	27 (7.8)
Tubal Ligation	10 (11.4)	9 (10.1)	10 (11.8)	1 (1.2)	3 (3.4)	23 (6.6)
Bronchitis NOS	8 (9.1)	9 (10.1)	2 (2.4)	4 (4.7)	3 (3.4)	18 (5.2)

NOS = not otherwise specified, NIDDM = noninsulin-dependent diabetes mellitus, GERD = gastroesophageal reflux disease, NEC = not elsewhere classified.

Subjects were counted once per condition/disease and were assigned using MedDRA.

[a] Table summarizes relevant medical history or concurrent disease for greater than 10% of subjects in any treatment group.

[b] Subjects who had hypertension assigned as either hypertension NOS or essential hypertension.

[c] Subjects who had hypercholesterolemia and hyperlipidemia were assigned either the cardiovascular or endocrine body system.

[d] Subjects who were post-menopausal were assigned either the endocrine or genito-urinary body systems.

Reference Documentation: Table 14.6

The treatment groups were fairly well balanced. Nothing in the table seems unusual.

2.2.4 Concomitant medications: are shown in the table below.

Table 11: Most Common Concomitant Medications Used During Double-blind Treatment - Safety Population

Medication	Placebo N = 88	80 mg N = 89	120 mg N = 85	160 mg N = 85	640 mg N = 87	Total N=346
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects Receiving Any Medication	65 (73.9)	70 (78.7)	65 (76.5)	67 (78.8)	66 (75.9)	268 (77.5)
Other Analgesics and Antipyretics	11 (12.5)	10 (11.2)	21 (24.7)	15 (17.6)	19 (21.8)	65 (18.8)
Propionic Acid Derivatives	16 (18.2)	13 (14.6)	16 (18.8)	19 (22.4)	9 (10.3)	57 (16.5)
Platelet Aggregation Inhibitors Exc Heparin	13 (14.8)	16 (18.0)	11 (12.9)	12 (14.1)	16 (18.4)	55 (15.9)
Cholesterol and Triglyceride Reducers	10 (11.4)	18 (20.2)	13 (15.3)	8 (9.4)	14 (16.1)	53 (15.3)
Nonsteroidal Antiinflammatory/Antirheumatic Products	9 (10.2)	8 (9.0)	11 (12.9)	12 (14.1)	8 (9.2)	39 (11.3)
Multivitamins, Plain	9 (10.2)	9 (10.1)	7 (8.2)	12 (14.1)	7 (8.0)	35 (10.1)
Oral Blood Glucose Lowering Drugs	9 (10.2)	12 (13.5)	6 (7.1)	8 (9.4)	9 (10.3)	35 (10.1)
Antihistamines for Systemic Use	9 (10.2)	8 (9.0)	8 (9.4)	6 (7.1)	5 (5.7)	27 (7.8)
Other Plain Vitamin Preparations	8 (9.1)	5 (5.6)	6 (7.1)	7 (8.2)	3 (3.4)	21 (6.1)
Estrogens	7 (8.0)	4 (4.5)	6 (7.1)	3 (3.5)	5 (5.7)	18 (5.2)
Proton Pump Inhibitors	2 (2.3)	3 (3.4)	6 (7.1)	5 (5.9)	3 (3.4)	17 (4.9)
H_2 Receptor Antagonists	2 (2.3)	5 (5.6)	5 (5.9)	3 (3.5)	3 (3.4)	16 (4.6)
Antidepressants	4 (4.5)	2 (2.2)	3 (3.5)	3 (3.5)	6 (6.9)	14 (4.0)
Ascorbic Acid, Inc Combinations	7 (8.0)	4 (4.5)	6 (7.1)	2 (2.4)	2 (2.3)	14 (4.0)
Calcium	4 (4.5)	6 (6.7)	2 (2.4)	3 (3.5)	3 (3.4)	14 (4.0)
Antacids	5 (5.7)	3 (3.4)	3 (3.5)	2 (2.4)	5 (5.7)	13 (3.8)
All Other Therapeutic Products	4 (4.5)	5 (5.6)	4 (4.7)	1 (1.2)	1 (1.1)	11 (3.2)
Opioids	1 (1.1)	2 (2.2)	5 (5.9)	1 (1.2)	2 (2.3)	10 (2.9)
Vitamin B Complex, Inc Combinations	5 (5.7)	1 (1.1)	1 (1.2)	1 (1.2)	0	3 (<1.0)

Inc = including, Exc = excluding.
Table summarizes concomitant medications for greater than 5% of subjects in any treatment group.
Medications coded using WHODRUG dictionary 1999.
Reference Documentation: Table 14.8.2

The majority of patients were receiving at least 1 concomitant medication. The groups were well balanced.

2.2.5 Mean trough blood levels

A substudy was conducted to measure trough levels of propranolol concentrations in a subgroup of 60 patients from 5-10 randomly selected study sites. The means are shown in the following figure.

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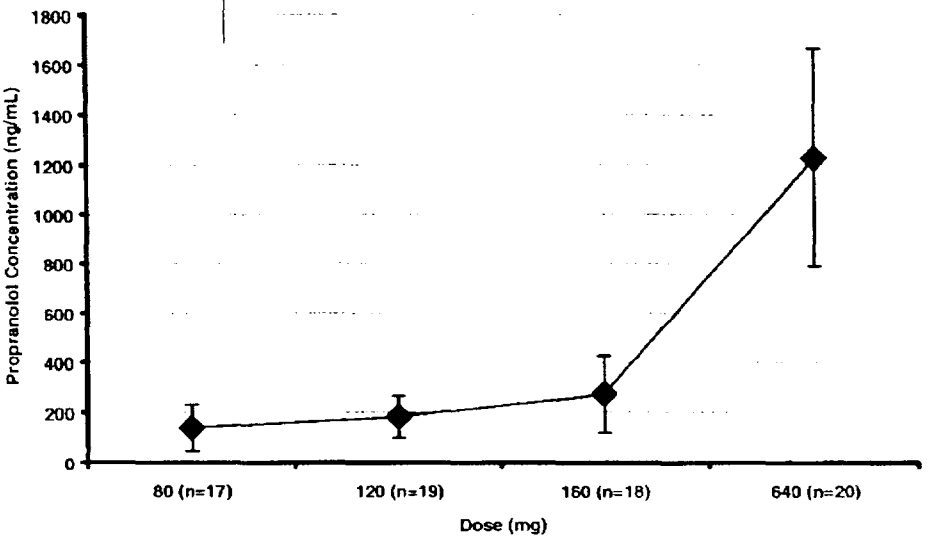
Figure 3: 3003 — Week 8 Dose Versus Mean Trough Propranolol Concentrations



Reference Documentation: Table 14.17

2.3 Efficacy

2.3.1.Study discontinuations

The table below shows the number and percent of all premature study discontinuations.

Number and (percent) of patients

	placebo	— 80	— 120	— 160	— 640
Randomized	88	89	85	85	87
Completed study	66 (75)	73 (82)	72 (85)	73 (86)	72 (83)
Prematurely discontinued	22 (25)	16 (18)	13 (15)	12 (14)	15 (17)

More placebo patients prematurely discontinued compared to — patients. Dropouts were similar across — dose groups.

2.3.2 Primary endpoint: (data tables from sponsor's study report)

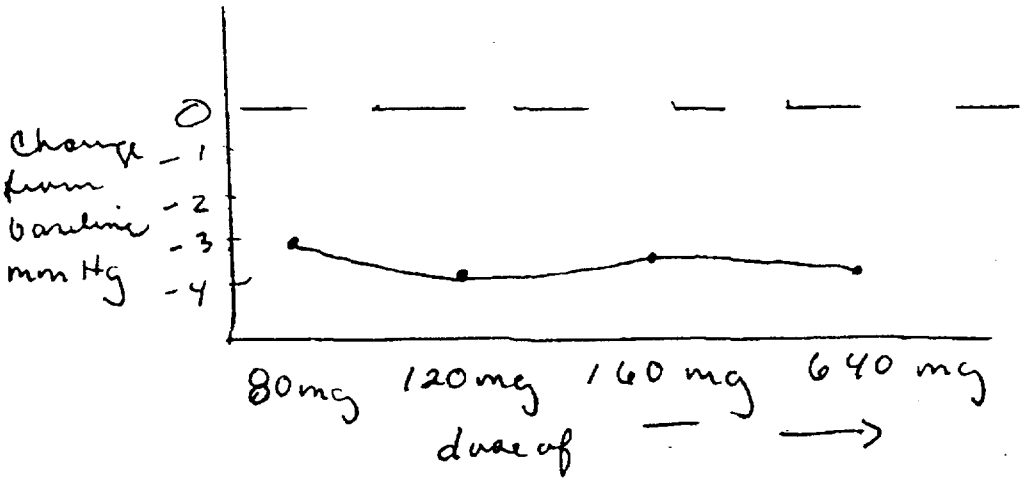
Mean changes from baseline at endpoint for morning diastolic blood pressure are shown below.

Table 13: Adjusted Mean Change in Sitting Morning Diastolic Blood Pressure - Analysis of Covariance

Mean Sitting Diastolic Blood Pressure (AM)	Placebo N = 84	80 mg N = 88	120 mg N = 84	160 mg N = 84	640 mg N = 87	P-value[a]
Intent-to-Treat Population						
Change From Baseline to Endpoint[b,c]						
N	84	88	84	84	87	
Adjusted Mean Change	-6.98	-10.09	-11.04	-10.43	-10.68	0.018
95% Confidence Interval	(-8.89, -5.08)	(-11.96, -8.22)	(-12.95, -9.13)	(-12.36, -8.51)	(-12.58, -8.78)	
p-value	NA	0.064	0.009	0.035	0.020	

[a]P-value for overall comparison among treatments from ANCOVA indicated in c.
[b]Baseline is Week 0. The Endpoint is Week 8 or if the subject discontinued the double-blind treatment phase prior to Week 8, the Endpoint is the last post treatment measurement taken. Hence, this analysis is based on LOCF to impute the missing Week 8 data.
[c]Adjusted mean change and 95% confidence interval were calculated from ANOVA on change from Baseline to Endpoint with factors for treatment, center, and Baseline values as a covariate. P-value was evaluated for comparison between placebo group and that treatment group from Dunnett's test.

The placebo subtracted changes for — 80 mg, 120 mg, 160 mg and 640 mg were -3.1 mmHg, -4.1 mmHg, -3.5 mmHg, and -3.7 mmHg, respectively. These changes are shown in the figure below.



All doses of — except the 80 mg (although it was close), were significantly better than placebo, but were indistinguishable from one another.

Overall, — was significantly better than placebo in lowering diastolic blood pressure at peak drug concentration, but there was little difference between doses (over an 8-fold dose range).

Change from baseline at week 8

There was little difference in diastolic blood pressure lowering effect of — , when one evaluates only at those patients who stayed on drug for the full 8 weeks (shown in the table below) compared to the intent-to-treat population.

Table 13: Adjusted Mean Change in Sitting Morning Diastolic Blood Pressure - Analysis of Covariance

Mean Sitting Diastolic Blood Pressure (AM)	Placebo N = 84	80 mg N = 88	120 mg N = 84	160 mg N = 84	640 mg N = 87	P-value[a]
Change From Baseline to Week 8[c,d]						
N	72	78	77	79	79	
Adjusted Mean Change	-7.70	-11.44	-11.76	-10.65	-11.23	0.027
95% Confidence Interval	(-9.73, -5.66)	(-13.39, -9.49)	(-13.70, -9.82)	(-12.61, -8.70)	(-13.19, -9.27)	
p-value	NA	0.025	0.013	0.104	0.037	

2.3.3 Secondary endpoints

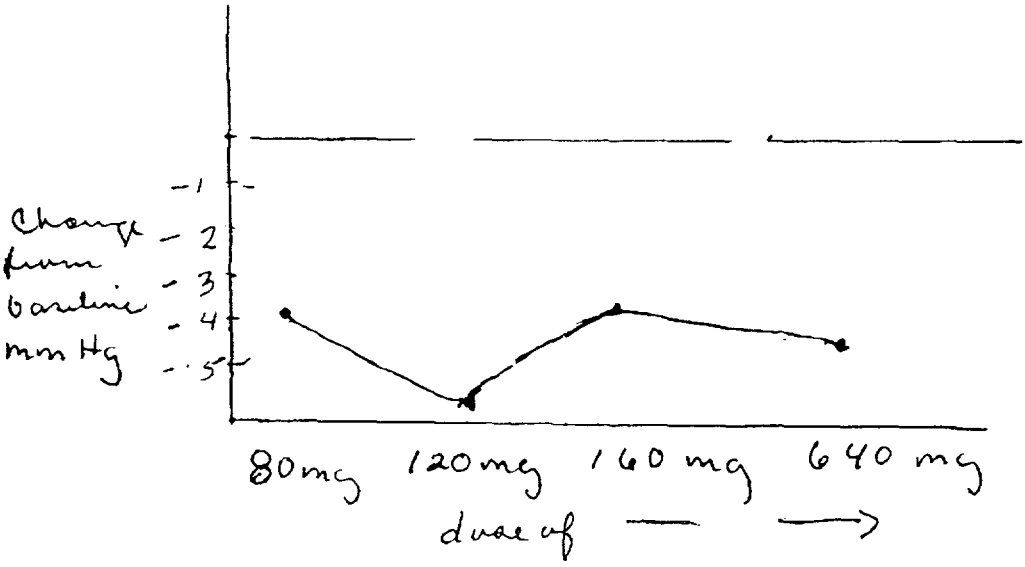
Secondary endpoints included sitting blood pressure recorded in the evening (PM) blood pressures, and pulse rate.

Table 14.2.2.1
Analysis of Covariance on Change from Baseline to Endpoint for the Secondary Efficacy Parameters
Intent-to-Treat Population

Parameter/Statistic (a)	Placebo (N = 84)	80 mg (N = 88)	120 mg (N = 84)	160 mg (N = 84)	640 mg (N = 87)	P-value (b)
Mean Sitting DBP-pm						
N	75	79	78	82	80	
Adjusted Mean Change	-7.76	-11.35	-13.52	-11.16	-12.23	0.001
95% CI	(-9.70, -5.81)	(-13.24, -9.46)	(-15.21, -11.42)	(-13.02, -9.30)	(-14.13, -10.33)	
P-value	NA	0.026	0.000	0.035	0.003	
Mean Sitting SBP-am						
N	84	88	84	84	87	
Adjusted Mean Change	-8.19	-11.96	-12.43	-12.17	-12.09	0.345
95% CI	(-11.60, -4.77)	(-15.30, -8.63)	(-15.85, -9.01)	(-15.63, -8.72)	(-15.48, -8.70)	
P-value	NA	0.311	0.227	0.277	0.289	
Mean Sitting SBP-pm						
N	75	79	78	82	80	
Adjusted Mean Change	-7.62	-14.00	-13.03	-11.29	-13.47	0.046
95% CI	(-11.01, -4.22)	(-17.30, -10.70)	(-16.35, -9.71)	(-14.54, -8.03)	(-16.78, -10.16)	
P-value	NA	0.023	0.070	0.314	0.041	
Mean Sitting PR-am						
N	84	88	84	84	87	
Adjusted Mean Change	-1.99	-6.13	-6.58	-8.84	-10.38	0.000
95% CI	(-3.64, -0.33)	(-7.74, -4.51)	(-8.64, -5.33)	(-10.52, -7.17)	(-12.02, -8.73)	
P-value	NA	0.001	0.000	0.000	0.000	

Note: Baseline is Week 0. Endpoint is Week 8 or if the subject discontinued the double-blind treatement phase prior to Week 8, the last post-treatment measurement taken. Hence, this analysis is based on LOCF to impute for missing Week 8 data.
(a) Adjusted mean and 95% CI calculated from ANOVA on change from baseline to Endpoint with factors for treatment, center and baseline values as a covariate. P-value for comparison between placebo group and that treatment group from Dunnett's test.
(b) P-value for overall comparison among treatments from ANCOVA indicated in (a).
(c) Mean sitting BPRP is the mean sitting blood pressure-pulse rate product= mean sitting SBP multiplied by mean sitting Pulse Rate.

Sitting diastolic blood pressure PM readings: the adjusted mean changes from baseline at trough drug concentration were significantly better than placebo for all drug dose levels. There was little clinical evidence of a dose response. The placebo subtracted changes for — 80 mg, 120 mg, 160 mg and 640 mg were –3.6mmHg, -5.6mmHg, -3.4mmHg, and –4.5mmHg, respectively. These changes are shown in the figure below.



Mean sitting systolic blood pressure AM and PM readings: the adjusted mean changes from baseline at peak drug concentration were numerically but not statistically significantly better than placebo for all drug dose levels. However, the effect at trough was significant for — 80 mg and 640 mg dose groups.

Mean sitting pulse rate AM readings: — significantly lowered pulse rate for all dose groups with some sign of a dose response. The drug effect on pulse rate at trough (<u>not</u> shown in the above table) was similar to the effect at peak.

In conclusion, — was significantly better than placebo in lowering diastolic blood pressure. Its effect on systolic blood pressure tended to be less impressive.

3.0 Safety

<u>3.1 Deaths, serious adverse events, discontinuations for safety,</u>

<u>Deaths</u>
There were no deaths reported for this study.

<u>Serious adverse events</u>
There were 5 patients who reported serious adverse events. These are shown in the table below.

Table 35: List of Serious Adverse Events During Double-blind Treatment

Study Drug	Subject ID	G/A	SAE	Severity	Day* of Onset	Action Taken	Relationship to Study Drug	Outcome
80 mg	28-0001	M/44	Musculoskeletal pain	Moderate	49	Discontinued, hospitalization	None	Recovered
160 mg	09-0008[a]	M/61	Myocardial infarction	Severe	77	Hospitalized	None	Recovered
120 mg	22-0017	M/40	Diverticulitis NOS	Severe	34	Discontinued, non-drug therapy, hospitalization	None	Recovered
			Gastrointestinal disorder NOS (ruptured sigmoid)	Severe	34	Discontinued, non-drug therapy, hospitalization	None	Recovered
			Abscess NOS	Severe	34	Discontinued, non-drug therapy, hospitalization	None	Recovered
120 mg	31-0014	M/57	Chest pressure sensation	Severe	57	Discontinued, concomitant medication, non-drug therapy, hospitalization	None	Recovered
			Dyspnea NOS	Severe	57	Discontinued, concomitant medication, non-drug therapy, hospitalization	None	Recovered
Placebo	23-0035	M/63	Cerebrovascular accident NOS	Severe	22	Discontinued, hospitalization	None	Recovered

G= gender, A = age (years), NOS = not otherwise specified
* Relative day is the number of days relative to the first dose of double-blind treatment
[a] The SAE of myocardial infarction for Subject No. 09-0008 was inadvertently left out of Appendices 16.2.7.1 and 16.2.7.2. A narrative for this subject is provided in Section 12.3.4
Reference Documentation: Appendices 16.2.4.1 and 16.2.7.2

Serious events included musculoskeletal pain, MI (occurring 7 days after patient completed the study), diverticulitis with abscess and ruptured sigmoid, chest pressure and dyspnea, and a stroke.

Discontinuations

A total of 26 patients (20 — and 6 placebo) dropped out of double blind treatment because of an adverse event. These are shown in the table below.

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Table 38: Treatment-emergent Adverse Events Resulting in Termination During Double-blind Treatment - Safety Population

Preferred Term[a]	Placebo N = 88	80 mg N = 89	120 mg N = 85	160 mg N = 85	640 mg N = 87	Total RelPro N = 346
Number of Subjects With Any AE Resulting in Termination	6 (6.8)	6 (6.7)	3 (3.5)	1 (1.2)	10 (11.5)	20 (5.8)
Insomnia NEC	0	0	0	0	3 (3.4)	3 (0.9)
Dyspnea NOS	1 (1.1)	1 (1.1)	1 (1.2)	0	1 (1.1)	3 (0.9)
Chest Pressure Sensation	0	0	1 (1.2)	0	1 (1.1)	2 (0.6)
Edema NOS	0	1 (1.1)	0	0	1 (1.1)	2 (0.6)
Abdominal Pain NOS	0	1 (1.1)	0	0	1 (1.1)	2 (0.6)
Fatigue	1 (1.1)	0	0	0	2 (2.3)	2 (0.6)
Musculoskeletal Pain	0	1 (1.1)	0	0	1 (1.1)	2 (0.6)
Dermatitis NOS	0	1 (1.1)	1 (1.2)	0	0	2 (0.6)
Cardiac Disorder NOS	0	1 (1.1)	0	0	0	1 (0.3)
Lower Limb Edema	0	0	0	1 (1.2)	0	1 (0.3)
Sinus Bradycardia	0	0	0	0	1 (1.1)	1 (0.3)
Constipation	0	0	0	0	1 (1.1)	1 (0.3)
Diarrhea NOS	0	0	0	0	1 (1.1)	1 (0.3)
Diverticulitis NOS	0	0	1 (1.2)	0	0	1 (0.3)
Gastrointestinal Disorder NOS	0	0	1 (1.2)	0	0	1 (0.3)
Nausea	2 (2.3)	0	0	0	1 (1.1)	1 (0.3)
Fatigue Aggravated	0	1 (1.1)	0	0	0	1 (0.3)
Pain NOS	0	0	0	0	1 (1.1)	1 (0.3)
Abscess NOS	0	0	1 (1.2)	0	0	1 (0.3)
Herpes Viral Infection NOS	0	0	0	0	1 (1.1)	1 (0.3)
Arthralgia	0	1 (1.1)	0	0	0	1 (0.3)
Back Pain	0	0	1 (1.2)	0	0	1 (0.3)
Dizziness (Exc Vertigo)	0	0	0	0	1 (1.1)	1 (0.3)
Headache NOS	2 (2.3)	0	0	0	1 (1.1)	1 (0.3)
Hypoesthesia	0	0	0	0	1 (1.1)	1 (0.3)
Rales	0	1 (1.1)	0	0	0	1 (0.3)
Cerebrovascular Accident NOS	1 (1.1)	0	0	0	0	0
Rash Erythematous	1 (1.1)	0	0	0	0	0
Hypertension NOS	1 (1.1)	0	0	0	0	0
Tachycardia NOS	1 (1.1)	0	0	0	0	0
Taste Disturbance	1 (1.1)	0	0	0	0	0
Vomiting NOS	1 (1.1)	0	0	0	0	0

NOS = not otherwise specified, Exc = excluding, NEC = not elsewhere classified.
[a] Preferred terms were assigned using MedDRA.
Reference Documentation: Appendix 16.1.9.2.2.2

The patient (23-0013) who reported flushing and upper and lower limb edema is missing from the above table. This patient reported these events 5 days before starting double blind therapy (randomized to —— 80 mg). She discontinued 3 days after starting study drug and recovered. The

sponsor did not include her in the list of patients who withdrew for adverse events because the events were reported prior to the patient starting double blind drug.

Adverse events leading to dropout reported by at least 2 — patients include insomnia (3), dyspnea (3), and chest pressure sensation, edema, abdominal pain, fatigue, musculoskeletal pain, dermatitis (2 patients each). Patients randomized to — 640 mg were more likely to drop out because of an adverse event compared to placebo (placebo subtracted drop out rate 4.7%) as well as the other — dose groups. Insomnia was the most cited reason for drop out in the — 640 mg dose group (3.4%).

All adverse events

The table below shows adverse events by body systems (in bold) and those adverse events reported by at least 3 subjects in at least 1 active treatment groups.

No. and (percent) of patients

	Placebo N=88	— 80mg N=89	— 120mg N=85	— 160mg N=85	— 640mg N=87
Any ae	45 (51)	45 (51)	44 (52)	38 (45)	49 (56)
Blood and lymph	**0**	**1**	**0**	**1**	**0**
Cardiac disorders	**8 (9)**	**7 (8)**	**4 (5)**	**10 (12)**	**6 (7)**
Cardiac disorders nos	0	3	1	3	0
Lower limb edema	0	1	0	4	1
Upper limb edema	0	1	0	3	0
Ear and labyrinth	**0**	**2 (2)**	**1 (1)**	**1 (1)**	**2 (2)**
Eye disorders	**1**	**2**	**1**	**0**	**0**
GI disorders	**18 (21)**	**9 (10)**	**8 (9)**	**7 (8)**	**16 (18)**
Constipation	0	3	1	0	2
Diarrhea	5	1	3	1	1
Nausea	7	2	2	1	4
General disorders	**9 (10)**	**5 (6)**	**8 (9)**	**5 (6)**	**14 (16)**
Fatigue	3	4	6	3	8
Nasopharyngitis	1	3	1	1	2
Injury and poisoning	**2 (2)**	**1 (1)**	**0**	**2 (2)**	**3 (3)**
Metabolism and nutrition disorders	**4 (5)**	**2 (2)**	**3 (4)**	**1 (1)**	**0**
Musculoskeletal, connective tissue, bone	**10 (11)**	**9 (10)**	**6 (7)**	**8 (9)**	**4 (5)**
Arthralgia	2	1	0	2	3
Nervous system	**18 (21)**	**12 (14)**	**18 (21)**	**13 (15)**	**22 (25)**
Dizziness other than vertigo	2	6	3	3	5

Headache	12	4	11	7	7
Insomnia	3	0	2	2	7
Psychiatric disorders	**2 (2)**	**3 (3)**	**5 (6)**	**1 (1)**	**1 (1)**
Renal and urinary	**0**	**2 (2)**	**3 (4)**	**0**	**2 (2)**
Repro. and breast	**0**	**1 (1)**	**1 (1)**	**2 (2)**	**0**
Respiratory	**5 (6)**	**8 (9)**	**4 (5)**	**3 (4)**	**7 (8)**
dyspnea	4 (5)	2 (2)	1 (1)	1 (1)	3 (3)
Skin disorders	**5 (6)**	**4 (5)**	**3 (4)**	**1 (1)**	**1 (1)**
Dermatitis nos	1 (1)	3 (3)	1 (1)	0	1 (1)
Surgical and medical procedures	**2 (2)**	**0**	**0**	**3 (4)**	**1 (1)**
Vascular disorders	**2 (2)**	**2 (2)**	**2 (2)**	**1 (1)**	**1 (1)**

Table 14.33.2

The most noteworthy events (events that were reported more often by patients on — compared to patients on placebo) include fatigue, dizziness excluding vertigo, insomnia, constipation, lower limb edema, and upper limb edema.

Adverse events by age, gender, and race (see attachments)

Age

The numbers of patients by age group were 135 for ages 30-49 yrs, 217 for ages 50-64, 76 for ages 65 yrs and old, and 6 missing.

No. and (percent) of patients reporting an event

	30-49 yrs		50-64 yrs		≥ 65 yrs	
	Pl N=25	— + N=110	Pl N=51	— + N=166	Pl N=10	— + N=66
No. of pts reporting at least 1 event	14 (56)	67 (61)	23 (45)	77 (46)	7 (70)	30 (45.5)

+all dose groups combined

While there is no indication that there are adverse events associated with age, the number of patients in the different age categories are low and the number of reported events are relatively few and the patients were not randomized by age.

Gender

A total of 187 females and 247 males were randomized.

No. and (percent) of patients reporting an event

	Female		Male	
	PL N=36	— + N=151	PL N=52	— + N=195
No. of pts reporting at least 1 event	22 (61)	77 (51)	23 (44)	99 (51)

+all dose groups combined

There is no indication that gender influenced the reporting of adverse events. However, the caveats for the age categories apply for the gender analysis as well.

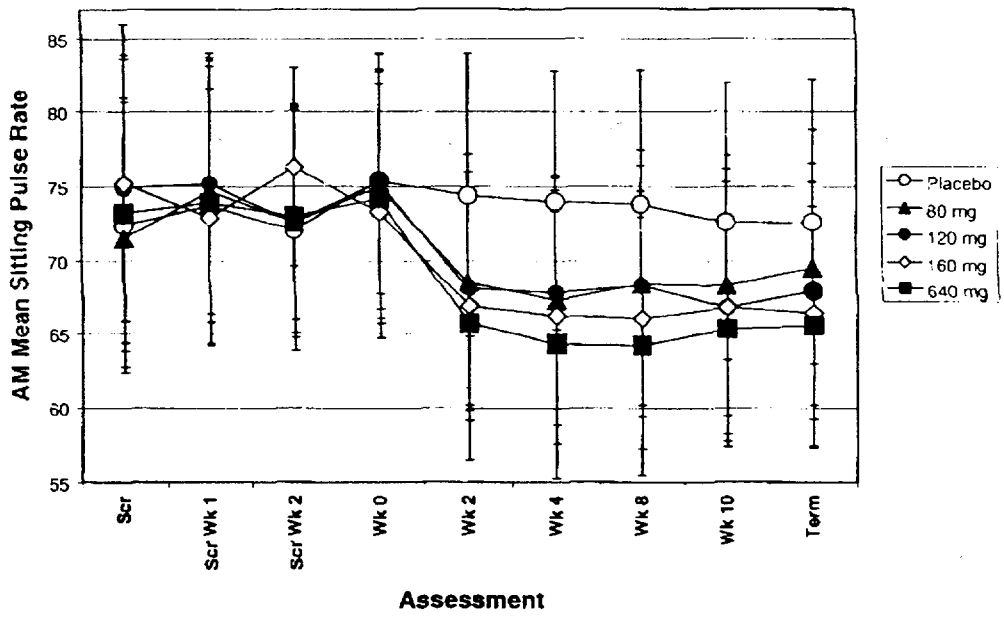
Race

There were 74 black and 352 white/hispanic patients randomized (and 8 not identified). No conclusions can be drawn about the influence of race on the reporting of adverse events in patients taking [redacted].

Heart rate

Peak effect of [redacted] on pulse rate by dose at peak effect is shown below by dose.

Figure 7: Morning Mean Sitting Pulse Rate



Scr = screen, Wk = week, Term = Termination
Error bars represent standard deviation
Reference Documentation: Table 14.20

As expected, heart rate decreased substantially from baseline in all active treatment groups compared to placebo.

Laboratory values

Hematology

Mean changes from baseline at endpoint for selected hematology parameters are shown below. The tables include only those patients with both pre and post baseline values. Percent lymphocytes and neutrophils are excluded because there were too few patients with data.

Mean changes (SD) from baseline

	Placebo	— 80mg	— 120mg	— 160mg	— 640mg
Hematocrit %	1.12 (2.45)	0.35 (2.74)	0.88 (2.82)	0.71 (2.31)	0.68 (2.81)
Hemoglobin g/dl	-0.15 (0.6)	-0.30 (0.86)	-0.24 (0.72)	-0.27 (0.71)	-0.21 (0.71)
Platelets k/mm3	-21.5 (43.64)	-28.0 (40.96)	-30.8 (38.49)	-27.2 (34.92)	-37.3 (39.40)
White blood cells k/mm3	-0.234 (1.35)	-0.241 (1.29)	-0.079 (1.46)	0.179 (1.39)	-0.397 (1.36)

Table 14.37

The tables below shows the number of patients who had normal hematology parameters at screening which became low (table 40) or high (table 41) at endpoint. Only those parameters with a minimum of 2 patients in at least 1 treatment group are included.

Table 40: Normal to Low Shifts in Hematology Laboratory Values From Screening to Termination - Safety Population

Laboratory Parameter	Placebo N=88	80 mg N=89	120 mg N=85	160 mg N=85	640 mg N=87
	n (%)	n (%)	n (%)	n (%)	n (%)
Red Blood Cell ($10^6/mm^3$)	3 (3.4)	6 (6.7)	7 (8.2)	1 (1.2)	2 (2.3)
Hematocrit (%)	0	3 (3.4)	1 (1.2)	1 (1.2)	0
Hemoglobin (g/dL)	1 (1.1)	2 (2.2)	0	1 (1.2)	2 (2.3)
Platelet Count ($10^3/mm^3$)	0	1 (1.1)	1 (1.2)	0	3 (3.4)
White Blood Cells ($10^3/mm^3$)	0	3 (3.4)	0	1 (1.2)	1 (1.1)

Low = below the lower limit of the reference range.
Note: Table summarizes normal to low shifts for at least 2 subjects in any treatment group.
Reference Documentation: Table 14.39

Table 41: Normal to High Shifts in Hematology Laboratory Values From Screening to Termination - Safety Population

Laboratory Parameter	Placebo N=88	80 mg N=89	120 mg N=85	160 mg N=85	640 mg N=87
	n (%)	n (%)	n (%)	n (%)	n (%)
White Blood Cells ($10^3/mm^3$)	1 (1.1)	1 (1.1)	2 (2.4)	5 (5.9)	1 (1.1)
Hematocrit (%)	3 (3.4)	0	3 (3.5)	1 (1.2)	3 (3.4)
Hemoglobin (g/dL)	2 (2.3)	0	0	0	2 (2.3)

High = above the upper limit of the reference range.
Note: Table summarizes normal to high shifts for at least 2 subjects in any treatment group.
Reference Documentation: Table 14.39

While there are differences in the number (and percent) of patients with abnormalities for the different treatment groups, there is no indication that — has an adverse effect on hematology values.

Chemistry

Mean changes from baseline at endpoint for selected chemistry values are shown below.

Mean changes (SD) from baseline

	placebo	80mg	120mg	160mg	640mg
Alk phos U/L	1.5 (12.5)	1.8 (13.6)	-1.2 (11.86)	-1.9 (11.75)	-0.7 (12.33)
BUN mg/dl	-0.1 (4.42)	0.2 (3.88)	0.5 (4.76)	0.6 (3.97)	0.3 (3.79)
Creatinine mg/dl	0.03 (0.10)	0.03 (0.11)	0.03 (0.10)	0.03 (0.13)	0.03 (1.10)
SGOT U/L	-1.1 (6.74)	-1.2 (7.41)	-3.1 (10.96)	-2.7 (9.7)	-1.4 (6.57)
SGPT U/L	-3.5 (17.83)	-3.4 (10.93)	-5.2 (14.94)	-4.9 (12.2)	-3.8 (9.72)
Total bili mg/dl	0.02 (0.269)	-0.02 (0.18)	0.03 (0.198)	-0.01 (0.18)	0.03 (0.20)
Tiglycerides mg/dl	10.8 (111.8)	61.4 (190.1)	7.8 (116.7)	43.5 (163.9)	36.1 (187.1)

Table 14.38

Normal to low and normal to high shift tables are shown below.

Table 42: Normal to Low Shifts in Chemistry Laboratory Values From Screening to Termination - Safety Population

Laboratory Parameter	Placebo N=88	80 mg N=89	120 mg N=85	160 mg N=85	640 mg N=87
	n (%)	n (%)	n (%)	n (%)	n (%)
LDL - Cholesterol (mg/dL)	1 (1.1)	4 (4.5)	2 (2.4)	5 (5.9)	2 (2.3)
Calcium (mg/dL)	0	1 (1.1)	2 (2.4)	3 (3.5)	3 (3.4)
Chloride (mEq/L)	3 (3.4)	2 (2.2)	2 (2.4)	2 (2.4)	3 (3.4)
Creatinine Phosphokinase (U/L)	0	2 (2.2)	0	1 (1.2)	2 (2.3)
Glucose (mg/dL)	2 (2.3)	1 (1.1)	1 (1.2)	2 (2.4)	1 (1.1)
Phosphorus/Phosphate (mg/dL)	1 (1.1)	0	2 (2.4)	0	1 (1.1)
Uric Acid (mg/dL)	2 (2.3)	0	0	0	2 (2.3)

Low = below the lower limit of the reference range.
Note: Table summarizes normal to low shifts for at least 2 subjects in any treatment group.
Reference Documentation: Table 14.40

Table 43: Normal to High Shifts in Chemistry Laboratory Values From Screening to Termination - Safety Population

Laboratory Parameter	Placebo N=88 n (%)	80 mg N=89 n (%)	120 mg N=85 n (%)	160 mg N=85 n (%)	640 mg N=87 n (%)
Triglycerides (mg/dL)	4 (4.5)	9 (10.1)	10 (11.8)	9 (10.6)	15 (17.2)
Glucose (mg/dL)	5 (5.7)	10 (11.2)	5 (5.9)	5 (5.9)	9 (10.3)
Uric Acid (mg/dL)	4 (4.5)	5 (5.6)	5 (5.9)	4 (4.7)	7 (8.0)
Creatinine Phosphokinase (U/L)	6 (6.8)	6 (6.7)	3 (3.5)	2 (2.4)	6 (6.9)
LDH (U/L)	5 (5.7)	2 (2.2)	1 (1.2)	3 (3.5)	4 (4.6)
SGPT/ALT (U/L)	3 (3.4)	4 (4.5)	1 (1.2)	2 (2.4)	2 (2.3)
Alkaline Phosphatase (U/L)	2 (2.3)	0	2 (2.4)	2 (2.4)	2 (2.3)
BUN (mg/dL)	3 (3.4)	1 (1.1)	1 (1.2)	2 (2.4)	1 (1.1)
Phosphorus/Phosphate (mg/dL)	0	1 (1.1)	3 (3.5)	1 (1.2)	2 (2.3)
Total Cholesterol (mg/dL)	5 (5.7)	3 (3.4)	0	2 (2.4)	2 (2.3)
SGOT/AST (U/L)	0	4 (4.5)	0	0	2 (2.3)
Total Bilirubin (mg/dL)	1 (1.1)	0	2 (2.4)	0	0

High = above the upper limit of the reference range.
Note: Table summarizes normal to high shifts for at least 2 subjects in any treatment group.
Reference Documentation: Table 14.40

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The only parameter that stands out from placebo is triglycerides.

Two subjects (both received —— 120 mg) experienced hypokalemia, one reported as mild and one reported as moderate. Both were treated with potassium chloride.

In conclusion, patients taking —— › 640 mg were more likely to discontinue treatment for an adverse event than patients taking placebo or a lower dose of —— The reporting of an adverse event was similar across treatment groups with fatigue, dizziness (except vertigo), insomnia, constipation, lower limb and upper limb edema being reported more often in the active treatment groups. There is no evidence that this agent is more or less harmful than the other formulations of propranolol.

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Attachments

Table 30: Most Common Treatment-emergent Adverse Events During Double-blind Treatment by Age - Safety Population

Age Group Preferred Term	Placebo	80 mg	120 mg	160 mg	640 mg	Total
30 - 49	**25**	**28**	**32**	**25**	**25**	**110**
Number of Subjects With an AE	14 (56.0)	18 (64.3)	17 (53.1)	14 (56.0)	18 (72.0)	67 (60.9)
Headache NOS	4 (16.0)	2 (7.1)	5 (15.6)	3 (12.0)	4 (16.0)	14 (12.7)
Fatigue	0	1 (3.6)	3 (9.4)	1 (4.0)	2 (8.0)	7 (6.4)
Dizziness (Exc Vertigo)	0	3 (10.7)	1 (3.1)	1 (4.0)	2 (8.0)	7 (6.4)
Nausea	1 (4.0)	1 (3.6)	1 (3.1)	1 (4.0)	1 (4.0)	4 (3.6)
Insomnia NEC	0	0	2 (6.3)	1 (4.0)	1 (4.0)	4 (3.6)
Nasal Congestion	0	1 (3.6)	1 (3.1)	0	2 (8.0)	4 (3.6)
Cardiac Disorder NOS	0	3 (10.7)	0	0	0	3 (2.7)
Palpitations	0	0	1 (3.1)	0	2 (8.0)	3 (2.7)
Arthralgia	2 (8.0)	0	0	2 (8.0)	1 (4.0)	3 (2.7)
Hypoesthesia	0	0	0	1 (4.0)	2 (8.0)	3 (2.7)
Cough	0	2 (7.1)	1 (3.1)	0	0	3 (2.7)
50 - 64	**51**	**41**	**41**	**41**	**43**	**165**
Number of Subjects With an AE[a]	23 (45.1)	24 (58.5)	18 (43.9)	15 (36.6)	20 (46.5)	77 (46.4)
Fatigue	2 (3.9)	3 (7.3)	3 (7.3)	2 (4.9)	3 (7.0)	11 (6.6)
Headache NOS	4 (7.8)	2 (4.9)	4 (9.8)	3 (7.3)	2 (4.7)	11 (6.6)
Dizziness (Exc Vertigo)	2 (3.9)	3 (7.3)	2 (4.9)	2 (4.9)	1 (2.3)	8 (4.8)
Lower Limb Edema	0	1 (2.4)	0	3 (7.3)	1 (2.3)	5 (3.0)
Nasopharyngitis	1 (2.0)	3 (7.3)	0	0	2 (4.7)	5 (3.0)
Insomnia NEC	2 (3.9)	0	0	1 (2.4)	4 (9.3)	5 (3.0)
Sinusitis NOS	1 (2.0)	1 (2.4)	2 (4.9)	1 (2.4)	0	4 (2.4)
Back Pain	1 (2.0)	1 (2.4)	1 (2.4)	2 (4.9)	0	4 (2.4)
Urinary Frequency	0	2 (4.9)	1 (2.4)	0	1 (2.3)	4 (2.4)
Dyspnea NOS	3 (5.9)	0	1 (2.4)	0	3 (7.0)	4 (2.4)

Continued

Table 30 Most Common Treatment-emergent Adverse Events During Double-blind Treatment by Age - Safety Population (continued)

Age Group Preferred Term	Placebo	80 mg	120 mg	160 mg	640 mg	Total
≥65	10	18	11	18	19	66
Number of Subjects With an AE	7 (70.0)	3 (16.7)	8 (72.7)	8 (44.4)	11 (57.9)	30 (45.5)
Headache NOS	3 (30.0)	0	2 (18.2)	1 (5.6)	1 (5.3)	4 (6.1)
Diarrhea NOS	0	0	2 (18.2)	0	1 (5.3)	3 (4.5)
Fatigue	1 (10.0)	0	0	0	3 (15.8)	3 (4.5)
Sinus Bradycardia	0	0	0	1 (5.6)	1 (5.3)	2 (3.0)
Abdominal Distension	0	0	0	2 (11.1)	0	2 (3.0)
Constipation	0	0	1 (9.1)	0	1 (5.3)	2 (3.0)
Nausea	1 (10.0)	0	0	0	2 (10.5)	2 (3.0)
Dizziness (Exc vertigo)	0	0	0	0	2 (10.5)	2 (3.0)
Insomnia NEC	1 (10.0)	0	0	0	2 (10.5)	2 (3.0)

AE = adverse event, NOS = not otherwise specified, Exc = excluding, NEC = not elsewhere classified.

Note: Table summarizes AEs for ≥2% of the Total group who were ≥30 years of age. Percentages are based on the total number of subjects in the safety population by age category. Subjects are counted once per AE preferred term. The preferred term was assigned using MedDRA.

[a] The SAE of myocardial infarction for Subject No. 09-0008 was inadvertently left out of Appendices 16.2.7.1 and 16.2.7.2. A narrative for this subject is provided in Section 12.3.4.

Reference Documentation: Appendix 16.1.9.2.4

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Table 31: Most Common Treatment-emergent Adverse Events During Double-blind Treatment by Gender - Safety Population

Gender Preferred Term	Placebo	80 mg	120 mg	160 mg	640 mg	Total
Female	**36**	**39**	**39**	**34**	**39**	**151**
Number of Subjects With an AE	22 (61.1)	18 (46.2)	20 (51.3)	16 (47.1)	23 (59.0)	77 (51.0)
Headache NOS	8 (22.2)	1 (2.6)	5 (12.8)	3 (8.8)	2 (5.1)	11 (7.3)
Fatigue	1 (2.8)	1 (2.6)	2 (5.1)	2 (5.9)	3 (7.7)	8 (5.3)
Dizziness (Exc Vertigo)	2 (5.6)	1 (2.6)	0	1 (2.9)	4 (10.3)	6 (4.0)
Lower Limb Edema	0	0	0	3 (8.8)	1 (2.6)	4 (2.6)
Sinusitis NOS	2 (5.6)	0	2 (5.1)	1 (2.9)	1 (2.6)	4 (2.6)
Insomnia NEC	2 (5.6)	0	1 (2.6)	1 (2.9)	2 (5.1)	4 (2.6)
Cardiac Disorder NOS	0	1 (2.6)	0	2 (5.9)	0	3 (2.0)
Constipation	0	1 (2.6)	1 (2.6)	0	1 (2.6)	3 (2.0)
Diarrhea NOS	2 (5.6)	0	2 (5.1)	0	1 (2.6)	3 (2.0)
Urinary Tract Infection NOS	1 (2.8)	1 (2.6)	0	2 (5.9)	0	3 (2.0)
Arthralgia	0	1 (2.6)	0	1 (2.9)	1 (2.6)	3 (2.0)
Musculoskeletal Pain	1 (2.8)	0	1 (2.6)	1 (2.9)	1 (2.6)	3 (2.0)
Dyspnea NOS	3 (8.3)	0	0	1 (2.9)	2 (5.1)	3 (2.0)
Dermatitis NOS	0	2 (5.1)	1 (2.6)	0	0	3 (2.0)
Male	**52**	**50**	**46**	**51**	**48**	**195**
Number of Subjects With an AE[a]	23 (44.2)	27 (54.0)	24 (52.2)	22 (43.1)	26 (54.2)	99 (50.8)
Headache NOS	4 (7.7)	3 (6.0)	6 (13.0)	4 (7.8)	5 (10.4)	18 (9.2)
Fatigue	2 (3.8)	3 (6.0)	4 (8.7)	1 (2.0)	5 (10.4)	13 (6.7)
Dizziness (Exc Vertigo)	0	5 (10.0)	3 (6.5)	2 (3.9)	1 (2.1)	11 (5.6)
Nausea	3 (5.8)	1 (2.0)	2 (4.3)	1 (2.0)	3 (6.3)	7 (3.6)
Insomnia NEC	1 (1.9)	0	1 (2.2)	1 (2.0)	5 (10.4)	7 (3.6)
Nasopharyngitis	1 (1.9)	3 (6.0)	0	1 (2.0)	2 (4.2)	6 (3.1)
Cardiac Disorder NOS	0	2 (4.0)	1 (2.2)	1 (2.0)	0	4 (2.1)
Back Pain	2 (3.8)	2 (4.0)	1 (2.2)	1 (2.0)	0	4 (2.1)
Dyspnea NOS	1 (1.9)	2 (4.0)	1 (2.2)	0	1 (2.1)	4 (2.1)
Nasal Congestion	0	1 (2.0)	1 (2.2)	0	2 (4.2)	4 (2.1)

AE = adverse event, NOS = not otherwise specified, Exc = excluding, NEC = not elsewhere classified.

Note: Table summarizes AEs for ≥2% of the Total — group. Percentages are based on the total number of subjects in the safety population by age category. Subjects are counted once per AE preferred term. The preferred term was assigned using MedDRA.

[a] The SAE of myocardial infarction for Subject No. 09-0008 was inadvertently left out of Appendices 16.2.7.1 and 16.2.7.2. A narrative for this subject is provided in Section 12.3.4.

Reference Documentation: Appendix 16.1.9.2.5

Table 32: Most Common Treatment-emergent Adverse Events During Double-blind Treatment by Ethnic Origin - Safety Population

Ethnic Origin Preferred Term	Placebo	80 mg	120 mg	160 mg	640 mg	Total —
Black	12	19	15	12	16	62
Number of Subjects With an AE[a]	7 (58.3)	11 (57.9)	7 (46.7)	4 (33.3)	10 (62.5)	32 (51.6)
Dizziness (Exc Vertigo)	0	3 (15.8)	0	0	2 (12.5)	5 (8.1)
Headache NOS	1 (8.3)	1 (5.3)	2 (13.3)	1 (8.3)	3 (18.8)	7 (11.3)
Sinusitis NOS	1 (8.3)	0	1 (6.7)	0	1 (6.3)	2 (3.2)
Tinnitus	0	0	0	1 (8.3)	1 (6.3)	2 (3.2)
Nausea	0	0	0	0	2 (12.5)	2 (3.2)
Aggravated Fatigue	0	1 (5.3)	0	1 (8.3)	0	2 (3.2)
Hypoesthesia	0	0	0	0	2 (12.5)	2 (3.2)
Caucasian	63	52	55	55	58	220
Number of Subjects With an AE	33 (52.4)	27 (51.9)	32 (58.2)	27 (49.1)	33 (56.9)	119 (54.1)
Fatigue	3 (4.8)	4 (7.7)	6 (10.9)	3 (5.5)	7 (12.1)	20 (9.1)
Headache NOS	11 (17.5)	2 (3.8)	8 (14.5)	6 (10.9)	4 (6.9)	20 (9.1)
Insomnia NEC	3 (4.8)	0	2 (3.6)	2 (3.6)	6 (10.3)	10 (4.5)
Dizziness (Exc Vertigo)	2 (3.2)	2 (3.8)	2 (3.6)	2 (3.6)	3 (5.2)	9 (4.1)
Cardiac Disorder NOS	0	3 (5.8)	1 (1.8)	3 (5.5)	0	7 (3.2)
Nausea	7 (11.1)	2 (3.8)	2 (3.6)	1 (1.8)	2 (3.4)	7 (3.2)
Nasopharyngitis	1 (1.6)	3 (5.8)	1 (1.8)	1 (1.8)	1 (1.7)	6 (2.7)
Arthralgia	1 (1.6)	1 (1.9)	0	2 (3.6)	3 (5.2)	6 (2.7)
Back Pain	2 (3.2)	2 (3.8)	2 (3.6)	2 (3.6)	0	6 (2.7)
Lower Limb Edema	0	0	0	4 (7.3)	1 (1.7)	5 (2.3)
Diarrhea NOS	5 (7.9)	1 (1.9)	2 (3.6)	1 (1.8)	1 (1.7)	5 (2.3)
Dermatitis NOS	1 (1.6)	3 (5.8)	1 (1.8)	0	1 (1.7)	5 (2.3)
Hispanic	12	16	13	16	12	57
Number of Subjects With an AE	5 (41.7)	7 (43.8)	3 (23.1)	7 (43.8)	6 (50.0)	23 (40.4)
Constipation	0	1 (6.3)	0	0	1 (8.3)	2 (3.5)
Dizziness (Exc Vertigo)	0	1 (6.3)	0	1 (6.3)	0	2 (3.5)
Headache NOS	0	1 (6.3)	1 (7.7)	0	0	2 (3.5)

AE = adverse event, NOS = not otherwise specified. Exc = excluding, NEC = not elsewhere classified.

Note: Table summarizes AEs for ≥2% of the Total — group who were Black, Caucasian, or Hispanic. Percentages are based on the total number of subjects in the safety population by age category. Subjects are counted once per AE preferred term. The preferred term was assigned using MedDRA.

[a] The SAE of myocardial infarction for Subject No. 09-0008 was inadvertently left out of Appendices 16.2.7.1 and 16.2.7.2. A narrative for this subject is provided in Section 12.3.4.

Reference Documentation: Appendix 16.1.9.2.6

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Maryann Gordon
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