CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-438

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

NDA 21-438 **SUBMISSION DATE:** October 31, 2001

— Extended Release Capsules
80, 120, — (Propranolol HCl)
Reliant Pharmaceuticals, LLC
Liberty Corner, NJ **REVIEWER:** Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Original New Drug Application

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-438	Brand Name	Ext. Release Caps.
OCPB Division (I, II, III)	DPEI	Generic Name	Propranolol HCl
Medical Division	DCRDP	Drug Class	Beta-adrenergic receptor-blocking agent
OCPB Reviewer	Angelica Dorantes, Ph.D.	Indication(s)	Hypertension
OCPB Team Leader	Patrick Marroum, Ph.D.	Dosage Form	80, 120, capsules
		Dosing Regimen	Once a day
Date of Submission	November 2, 2001	Route of Administration	Oral
OCPB Estimated Due Date	June 2002	Sponsor	Reliant Pharmaceuticals
PDUFA Due Date	September 2, 2002	Priority Classification	Standard
Division Due Date	July 2002		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data,	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	5	4	
multiple dose:	X	1	1	
Patients-				
single dose:		1	1	
multiple dose:	X	1	1	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1	1	
pediatrics:				
geriatrics:	X	1	1	
renal impairment:				
hepatic impairment:				

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1	1	Propranolol trough levels
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	X	2	2	[redacted]
solution as reference:				
alternate formulation as reference:	X	2	2	
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	7	6	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	
Comments to be sent to the firm ?	X	To facilitate the review of this NDA, an electronic submission of the individual study tables included in Volume 1 and individual PK study reports are needed.
QBR questions (key issues to be considered)		1. Are the proposed dissolution methodology and release specifications acceptable? 2. Is food affecting the bioavailability of Vasopran ER Capsules? 3. Are the 80, 120, and 160 mg formulations dose proportional? 4. Is the clinical pharmacology and biopharmaceutic information included in the proposed labeling acceptable to OCPB?
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-438, HFD-850(Lee), HFD-110(McDonald), HFD-860(Dorantes, Marroum, Mehta), CDR (Biopharm)

EXECUTIVE SUMMARY

In this original NDA, the sponsor is seeking approval of three strengths of — (propranolol HCl) extended release capsules containing 80, 120, — is a synthetic beta-adrenergic receptor-blocking agent indicated for the management of hypertension —

— was reformulated as extended-release capsules (ERC), to provide a delayed sustained-release of propranolol HCl without an immediate release component of the drug. The new design was intended to be administered at bedtime and to provide a 3-5 hour delay followed by a sustained release of the active ingredient for approximately 14 hours. When taken at bedtime, the propranolol plasma levels which rise slowly attenuate the rapid increase in blood pressure and heart rate that precedes and follows waking. This increase is associated with the circadian variation in catecholamine secretion and in a renin release. The rise in plasma propranolol concentration after dosing parallels the circadian rise in morning blood pressure associated with target organ damage in patients with hypertensive and ischemic cardiovascular disease.

To support the approval of — extended release capsules, the sponsor conducted studies 3000, — 3002, 3006, and 3007; a pilot PK study and four pharmacokinetic/bioavailability studies to determine the dose-proportionality, food dumping-effect, bioavailability, single and steady-state pharmacokinetics of — extended release capsules in healthy subjects. Additionally, the sponsor evaluated the dose-proportionality and steady-state pharmacokinetics of — 80 mg, 120 mg, and 160 mg in patients with essential hypertension in pivotal clinical study 3003.

Study summaries are presented next:

- **Study No. 3000** entitled, *"A Phase I, Pilot Study to Evaluate the Safety and Preliminary Pharmacokinetics of — 80 mg and 160 mg in Healthy Volunteers"*.

  The primary objective of this pilot study was to evaluate the safety and preliminary pharmacokinetics of 80 mg and 160 mg of — Pharmacokinetic parameters Cmax, Tmax, t1/2, AUC0-72, and AUC0-last were derived from the plasma data. Neither dose of — demonstrated satisfactory pulsatile release characteristics in any subject. Propranolol release was fairly immediate, and the anticipated 4 to 5 hour delay prior to the release of the sustained release pulse was not evident. Therefore, further development of this formulation was stopped and a reformulated ER-product was used in future studies.

  Reviewer Comment: It should be noted that this reviewer considered that study 3000 did not contribute to the clinical pharmacology and biopharmaceutic evaluation of the to-be-marketed product, therefore, it was not reviewed.

- **Study No.** entitled, *"A Double-Blind, placebo-Controlled, Crossover Study to Assess — Dose Proportionality of — 80 mg, 120 mg, and 160 mg in Healthy Volunteers"*.

  This was a placebo controlled, four-period, crossover trial evaluating the dose proportionality — of oral — 80 mg, 120 mg, and 160 mg extended-release capsules in thirty-six healthy male and female subjects. The primary objectives of the study were to assess the efficacy and dose proportionality of — 80 mg, 120 mg, and 160 mg in healthy subjects.

  — to assess the safety of — 80 mg, 120 mg, and 160 mg in healthy subjects. The adjusted means for dose-normalized pharmacokinetic parameters AUC0–last, AUC0-8, and Cmax showed dose proportional increases following single dose administration of 80 mg, 120 mg, and 160 mg, — . The absorption lag time (Tlag) and Tmax were similar across all — dose groups.

- **Study No. 3002** entitled, *"A Randomized, Open-Label, Two-Period Cross-Over Study to Assess the Effect of Food on [redacted] Bioavailability in Healthy Adult Subjects"*.

  The primary objective of this study was to evaluate the effect of food on [redacted] bioavailability after oral administration of 640 mg of oral [redacted] given as four 160 mg [redacted] capsules at night (9:30-10:30 PM). Thirty-six healthy subjects were randomly assigned to one of two possible sequences. There was a 7-day washout period between doses. Cmax, Tmax, T1/2, AUC0-T, AUC0-inf, and Tlag were derived from the plasma data. A high fat meal increased the time to maximum concentration and increased the bioavailability of [redacted] This was evidenced by an approximate 4 hour delay in peak plasma concentrations and the 90% CI calculated from the ANOVA performed on the AUCs. Peak propranolol concentrations were not affected by a high fat meal (Cmax fasted 1003 ng/mL vs fed 1017 ng/mL). Despite the increased lag time in the fed condition, plasma propranolol concentrations increased during the morning hours in a clinically relevant manner characteristic of this formulation.

- **Study No. 3003** entitled, *"A Randomized, Double-Blind, Parallel, Placebo-Controlled, Multicenter Trial to Study the Efficacy, safety, and steady state Pharmacokinetics of [redacted] (Dose Levels: 80 mg, 120 mg, 160 mg, and 640 mg) in Patients with Essential Hypertension"*.

  The primary objective of this study was to assess the efficacy of [redacted] treatment in subjects with essential hypertension by evaluating the mean change from Baseline to Week 8 in morning sitting diastolic blood pressure. The secondary objectives of this study were: **1)** to assess the safety of [redacted], **2)** to determine the effect of treatment on the change from Baseline to Week 8 in mean sitting systolic blood pressure, pulse rate, and mean sitting blood pressure-rate product (mean sitting systolic blood pressure multiplied by the pulse rate) measured in the morning and evening, and mean sitting diastolic blood pressure measured in the evening; and **(3)** trough plasma samples were collected from a subgroup of subjects at Weeks 4 and 8 to evaluate the difference in plasma trough propranolol levels between dose groups. Subjects were randomized to one of the following five double-blind treatment groups: Placebo, [redacted] 80 mg/day, [redacted] 120 mg/day, [redacted] 160 mg/day, or [redacted] 640 mg/day.

  Trough plasma total propranolol levels increased in a dose-dependent manner with increasing [redacted] doses with significant differences among the treatment groups at both Week 4 and Week 8. A dose response relationship between [redacted] dose and the log of the mean trough level was confirmed. Pharmacodynamic analysis of efficacy parameters showed statistically significant correlations between the mean (of Weeks 4 and 8) trough total propranolol levels and change from Baseline to Endpoint in evening diastolic blood pressure, morning and evening pulse rate, and morning and evening BPRP. Regression analysis of natural log transformed (placebo group excluded) trough total propranolol levels and efficacy parameters indicated the same significant correlations. Age and gender appeared to be the only demographic and baseline characteristics associated with log-transformed trough level.

- **Study No. 3006** entitled, *"A Single and Multiple Dose, Two-Period, Cross-Over Study to Evaluate the Bioavailability and Safety of [redacted] 160 mg Relative to Inderal® LA 160 mg in Healthy, Adult Male subjects"*.

  This was a randomized, open-label, single-center, two-period, cross-over trial designed to evaluate the single and multiple dose bioavailability and safety of oral [redacted] 160 mg extended-release capsules relative to Inderal® LA 160 mg capsules in healthy, adult, male subjects. The [redacted] formulation was designed to have a release delay followed by sustained release of propranolol for up to 14 hours so that hypertensive patients, when dosed at bedtime, would be protected during the waking hours of the morning when vulnerability to target organ damage ischemic cardiovascular events is greatest. The results showed that [redacted] did indeed have a 2- to 4-hour release delay followed by clinically significant sustained plasma propranolol concentrations for a duration of 18 to 24 hours post dose following single and multiple dose (steady state) administrations.

- **Study No. 3007** entitled, *"A Single Dose, Two-Period, Cross-Over Study to Evaluate the Safety and Preliminary Pharmacokinetics of [redacted] 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 of — relative to 160 mg of Inderal® LA. This new formulation was intended to optimize plasma levels of propranolol in relation to circadian variations in blood pressure and heart rate. The pharmacokinetic parameters of AUC0-72hr and Cmax for — 160 mg (2268 ng/hr/mL and 121 ng/mL, respectively) were similar to Inderal® LA 160 mg (2414 ng/hr/mL and 154 ng/mL, respectively); however, the — 160 mg formulation resulted in a delayed release of propranolol of 2.5 hr (Tmax = 13.1 hr for — 160 mg and 10.6 hr for Inderal® LA 160 mg).

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the information included in original NDA 21-438 dated October 31, 2001 for — Extended Release Capsules. OCPB is of the opinion that the sponsor has provided appropriate information to satisfy the clinical pharmacology and biopharmaceutic requirements for an ER-product and NDA 21-438 for — Capsules is acceptable, provided the following dissolution and labeling comments are addressed.

- ***Dissolution:*** Based on the review of the submitted dissolution data, OCPB considers that the proposed dissolution method (i.e., USP Apparatus 2, speed of 50 rpm, and dissolution medium of 700 mL 0.1N HCl for 2 hrs, then pH change to 6.8 with addition of 200 mL of phosphates buffer), is acceptable. With respect to the proposed dissolution specifications, the data show that the proposed sampling time at 16 hour is not needed and the specifications for the 4, 6, and 10 hours are less than appropriate and are not acceptable. The specifications that are recommended for — capsules are as follow:

2 hrs	NMT	%
4 hrs	NMT	%
6 hrs	—	%
10hrs	—	%
20hrs	NLT	%

- ***Labeling:*** The clinical pharmacology information for propranolol that was included in the labeling is incomplete, especially with respect to metabolic and drug-drug interaction information. The sponsor should update the Pharmacokinetic section of the labeling and the following format is recommended:

  The Pharmacokinetics portion of the Clinical Pharmacology section of the package insert should present information for the Absorption, Distribution, Metabolism, and Excretion of propranolol. Following this, there should be a section with the heading Special Populations, where pharmacokinetic information under the subheadings of Geriatric, Pediatric, Gender, Race, Renal Insufficiency, Hepatic Impairment should be included. A section with the heading Drug-Drug Interactions is also needed. If there is PK/PD information, a "Population Pharmacokinetic/Pharmacodyamic" section should be added to the labeling. Where relevant information is lacking it should be so stated.

  Please note that the additional labeling information could be based on the sponsor studies or on information published in the literature.

  Also, please note that the specifics regarding the hepatic & renal impairment, metabolic and drug-interaction information for the labeling, are described in the Agency's Guidances titled;

  - *"Pharmacokinetics in Patients with Impaired Renal Function- Study Design, Data Analysis, and Impact on Dosing and*

Labeling",

- "*Pharmacokinetics in Patients with Impaired Hepatic Function- Study Design, Data Analysis, and Impact on Dosing and Labeling* (DRAFT)",
- "*In Vivo Drug Metabolism/Drug Interaction Studies- Study Design, Data Analysis, and Recommendations for Dosing and Labeling*", and
- "*Drug metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro*".

Please convey the Recommendation and comments as appropriate to the sponsor.

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

FT Initialed by Patrick Marroum, Ph.D. /S/

Briefing Day 8/6/02 (Mehta, Marroum, Dorantes, Venitz, Zimmerman, karkowsky)
cc: NDA 21-438, HFD-110, HFD-860 (Dorantes, Marroum, Mehta), and CDR (Biopharm).

QUESTION BASED REVIEW

1. How was the new propranolol control release formulation developed?

Reliant Pharmaceuticals, LLC has developed a new formulation composed of timed, sustained-release beads and has been designed to initiate release of propranolol HCl 3 to 4 hours after ingestion with a delayed, sustained drug release over a period of 12 to 16 hours following the lag time. The preparation is designed to release the active ingredient as a sustained release pulse after a controlled lag time for absorption into the gastrointestinal tract.

The inner layer functions as an extended release coating with the outer layer functioning to delay drug release 4 to 5 hours after ingestion.

PROPRANOLOL HCL CRR CAPSULES

The following tables present the unit dose and quantitative composition of the formulation that is proposed to-be-marketed and for which approval is requested.

Ingredient	Theoretical Quantity per capsule (mg)	Theoretical Quantity per capsule (mg)	Theoretical Quantity per capsule (mg)
	80 mg	120 mg	
Sugar Spheres NF			
Propranolol hydrochloride USP			
Povidone USP			
Ethylcellulose NF			
Hypromellose phthalate NF			
Diethyl phthalate NF			
Purified Water USP	*	*	*
	*	*	*
Total Fill Weight			

* Removed during processing

Ingredients	mg/capsule	
	80 mg (Size 3)	120 mg (Size 2)
Propranolol hydrochloride TSR Beads		
Hard Gelatin Capsules		

* Beads based on a theoretical assay of 46.75% w/w.
** Based on a theoretical empty capsule weight.

Reviewer Comment:

- *It should be noted that — was the name proposed in the original NDA submitted on October 31, 2001, however, — name was not accepted by the Division of Medication Errors and Technical support, Office of Drug Safety. Two new names were proposed and — was accepted as the final name for this propranolol extended release product. Therefore, in some parts of this review, the name — instead of — is being used.*
- *Please note that clinical pharmacology, biopharmaceutic and clinical studies (i.e., studies —3002, 3003, 3006, and 3007) were conducted with the proposed to-be-marketed 80, 120, and — formulations. Therefore, there was not need for bioequivalence studies to link clinical and commercial formulations.*

2. Are the proposed dissolution methodology and specifications acceptable?

The proposed dissolution methodology and specifications for — 80, 120, — capsules are as follow:

PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS FOR — 80, 120, — CAPSULES	
Variable	**Parameter**
Apparatus Type	USP Apparatus 2
Dissolution Medium	700 mL 0.1N HCl (2 hr.), pH change to 6.8 with addition of 200 mL buffer
Volume of Medium	700 mL with 0.1N HCl and 900 mL with pH 6.8 media
Temperature of Medium	37°C
Speed of Rotation	50 rpm
Sample Pull Times	2, 4, 6, 10, 16, and 20 hours
Specifications	2 hrs NMT 4 hrs 6 hrs 10hrs 16hrs NLT 20hrs NLT

The dissolution results for the lots of — extended release capsules used in bio-studies 3002, 3003, and 3006 are presented in the next table. A summary of the dissolution data for the stability lots is included in Attachment I.

STRENGTH	LOT No.	% DISSOLVED OF PROPRANOLOL				
		2 hrs	4 hrs	6 hrs	10 hrs	16 hrs
80 mg	PF261EA991 (n=12)					
120 mg	PF262EA988 (n=42)					
160 mg	PF263EA98 (n=12)					

Reviewer Comments:

- *Based on the review of the submitted dissolution data (limited data), OCPB considers that the proposed dissolution method is acceptable. With respect to the proposed dissolution specifications, the data show that the specification will not provide any additional information to the release characteristics of the product and is not needed and the specification ranges at 4, 6, and 10 hours are less than appropriate and are not acceptable. The specifications that are recommended for Extended Release capsules are based on the mean ± 10% data from the bio- and stability lots, and are as follow:* 2 hrs: NMT 4 hrs: NMT 6 hrs: 10hrs: and 20hrs:

3. What analytical methodology was used to determine propranolol ?

A ... was developed for propranolol plasma concentrations. This method was validated for propranolol over the concentration range of 2.00 to 200 ng/mL with a lower limit of quantitation equal to the lowest calibration level of ng/mL. The same assay was used for the determination of propranolol plasma concentrations in studies 3002, 3002, 3006, and 3007. The next table provides a validation summary.

VALIDATION SUMMARY FOR PROPRANOLOL					
Type of Assay	Matrix	Sensitivity of Method & Range (ng/ml)	Intra-Assay* Precision Range & Accuracy	Inter-Assay* Precision Range & Accuracy	Specificity
	Human Plasma/ heparin		1.2-1.4% 6.2%	1.2-3.3% 4.9%	No interferences noted

*coefficient of variation

Reviewer Comment:

- *The analytical methodology used to assay propranolol in the studies and the provided validation data are appropriate. Also, this submission included Quality Control data for the determination of propranolol in plasma. These Quality Control data showed that the accuracy and precision for propranolol is in the expected range for the used analytical methodology.*

4. What are the highlights of the pharmacokinetics of extended release capsules after single dose and at steady-state.

The following table presents an overall summary of propranolol pharmacokinetic parameters for the studies provided in the NDA.

		MEAN (SD) SINGLE DOSE PHARMACOKINETIC PARAMETERS FOR							
Dose	N	AUC0-inf (ng.hr/ml)	Cmax (ng/ml)	Tmax (hr)	T1/2 (hr)				
80 mg[b]	36	1569 (865)	80.5 (31.5)	12.2 (1.93)	9.5 (5.1)				
120 mg[b]	36	2413 (1287)	130 (52.3)	12.8 (2.4)	8.5 (4.7)				
160 mg[c]	80	3062 (1540)	162 (64.3)	12.6 (2.5)	8.1 (3.3)				
640 mg[d]	35	22179 (10869)	1017 (431.4)	15.4 (3.2)	8.2 (2.7)				
640 mg[e]	35	18975 (9593)	1003.2 (344)	11.5 (2.8)	8.4 (3.5)				
		MEAN (SD) MULTIPLE DOSE PHARMACOKINETIC PARAMETERS FOR							
Dose	N	AUC0-tss (ng.hr/ml)	Cmaxss (ng/ml)	Cminss (ng/ml)	Cavss (ng/ml)	Tmax (hr)	Tmin (hr)	Rac	Fi
160 mg[c]	35	3646 (1617)	248 (104)	58.9 (38)	151 (67)	12.6 (1.9)	7.3 (8.7)	1.8 (0.7)	131 (31.4)

[b]Includes Study Mean pharmacokinetic data
[c]Includes Studie 3006, and 3007 single and 3006 multiple mean pharmacokinetic data
[a]Includes Study 3002 Mean pharmacokinetic fed-data
[a]Includes Study 3002 Mean pharmacokinetic fasted-data

5. Does food have a dose-dumping effect on — formulation?

No, food does not have a dose-dumping effect, but it affects the bioavailability of —

A summary of the pharmacokinetic parameters and statistical analysis in fasted and fed conditions is presented below.

Summary of Mean (SD) Pharmacokinetic Parameters and Statistics for — 640 mg (n=35)

PHARMACOKINETICS			STATISTICS			
Parameter	**Fasted**	**Fed**	**Adjusted Mean Fasted***	**Adjusted Mean Fed***	**Ratio**	**90% CI**
AUC_{0-t} (ng.h/ml)	18584.8 (9031)	21825 (10617)	16295	19363	1.2	106-133%
AUC_{0-inf} (ng.h/ml)	18975 (9593)	22179 (10869)	16536	19661	1.2	106-133%
C_{max} (ng/ml)	1003 (344)	1017 (431)	936	930	1	89-111%

*Adjusted means and CIs displayed have been transformed from log to arithmetic scale

Reviewer Comments:

- *A high fat meal affected the rate of absorption and significantly increased the bioavailability of — There was approximately a 4 hour delay in peak plasma concentrations in the Fed group (approximately 1.3 hours longer that the Fasted group) and the 90% CI on the adjusted mean ratio of the AUCs (106-133%) were outside the acceptable range of 80% to 125%. However, propranolol Cmax concentrations were not affected by food (90% CI 89-111%).*
- *Although the statistical results showed that food affects the bioavailability of — this reviewer considers that there is an absorption-time-lag effect but not a dose-dumping effect with food. Therefore, from the clinical viewpoint, food may or may not have a relevant effect on the therapeutics of this product. For example, if a person takes — without food and the next day with food, the formulation lag-time period would be increased from 3-5 hours to at least 5-7hours, leaving that person with lower propranolol plasma levels for an extended period of time and increasing the risk of having lack of efficacy. However, if the person takes — always with food, then food would not affect the clinical outcome of this product. Based on these concerns, it is recommended to include in the labeling that — could be taken with or without food, but should be taken always under the same conditions.*

6. Are the 3 strengths of — Capsules dose proportional?

Yes, the results of studies 3002 (healthy subjects) and 3003 (hypertensive patients) showed dose proportional increases following single and multiple administration of — capsules. The results of study 3002 (single dose) are presented in the next table.

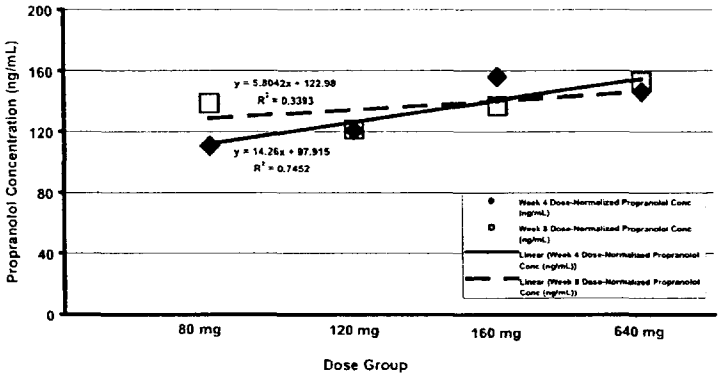
3002 Mean (SD) Pharmacokinetic Parameters and Statistics for — (n=36)

	PHARMACOKINETICS			STATISTICS				
Parameter	**Adjusted Mean (SD)**			**Normalized Adjusted Mean**			**Ratio & 90% CI**	
Parameter	**80 mg**	**120 mg**	**160 mg**	**80 mg**	**120 mg**	**160 mg**	**120/80 mg**	**160/80 mg**
AUC_{0-t} (ng.h/ml)	1443 (844)	2270 (1231)	3417 (2047)	14.6	15.4	17.4	1.1 96-116%	1.2 108-131%
AUC_{0-inf} (ng.h/ml)	1569 (865)	2413 (1287)	3589 (2081)	16.1	16.5	18.5	1.0 94-112%	1.1 105-125%
C_{max} (ng/ml)	80.5 (31.5)	130 (52.3)	177 (70.6)	0.9	1.0	1.0	1.1 98-116%	1.1 102-121%

Adjusted mean and 90% CI calculated from ANOVA on normalized, log-transformed data.
Adjusted means and CIs displayed have been transformed from log to arithmetic scale

The results of study 3003 in the hypertensive population are illustrated in the next graphic.

Dose Normalized Mean Trough Propranolol Concentrations



7. Is the clinical pharmacology information included in the proposed labeling acceptable?

A copy of the proposed labeling is included in Attachment II.

Reviewer Comment:

- *It is recommended that the sponsor revise the pharmacokinetic section of the labeling. The additional information could be based on the sponsor's data or in published literature. The following format should be followed and especial attention should be put in including additional metabolic and drug-drug interaction information for propranolol:*

The Pharmacokinetics portion of the Clinical Pharmacology section of the package insert should present information for the Absorption, Distribution, Metabolism, and Excretion of propranolol. Following this, there should be a section with the heading Special Populations, where pharmacokinetic information under the subheadings of Geriatric, Pediatric, Gender, Race, Renal Insufficiency, Hepatic Impairment should be included. A section with the heading Drug-Drug Interactions is also needed. If there is PK/PD information, a "Population Pharmacokinetic/Pharmacodyamic" section should be added to the labeling. Where relevant information is lacking it should be so stated.

Attachment I

Includes

NDA 21-438

"Summaries of Individual Studies & Dissolution Data:

Study No. — A Double-Blind, placebo-Controlled, Crossover Study to Assess — Dose Proportionality of — 80 mg, 120 mg, and 160 mg in Healthy Volunteers.

Study No. 3002: A Randomized, Open-Label, Two-Period Cross-Over Study to Assess the Effect of Food on — Bioavailability in Healthy Adult Subjects.

Study No. 3003: A Randomized, Double-Blind, Parallel, Placebo-Controlled, Multicenter Trial to Study the Efficacy, safety, and steady state Pharmacokinetics of — (Dose Levels: 80 mg, 120 mg, 160 mg, and 640 mg) in Patients with Essential Hypertension.

Study No. 3006: A Single and Multiple Dose, Two-Period, Cross-Over Study to Evaluate the Bioavailability and Safety of 160 mg Relative to Inderal LA 160 mg in Healthy, Adult Male subjects.

Study No. 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.

Analytical Methodology: Validation Summary for Propranolol and 4-Hydroxypropranolol.

Dissolution Data: Summary of Dissolution Data for the Stability Lots

Study Report Summary

Study No.

Study Title: A Double-Blind, placebo-Controlled, Crossover Study to Assess the — Dose Proportionality of — 80 mg, 120 mg, and 160 mg in Healthy Volunteers.

Principal Investigator/Investigation Site:

Objectives:

- The primary objectives of the study — dose proportionality of — 80 mg, 120 mg, and 160 mg in healthy subjects.
- Secondary objectives of this study — to assess the safety (as assessed by blood pressure measurements, electrocardiograms (ECGs), clinical laboratory evaluations, and physical examinations) of — 80 mg, 120 mg, and 160 mg in healthy subjects.

Study Population:

Healthy male and female between 18 and 40 years of age were enrolled in the study. An enrollment of 36 subjects was planned and 39 were enrolled. Any subjects withdrawn from the study before completion were replaced. The demographic characteristics are presented below.

Parameter	Statistic	(N = 39)
Age (years)	N	39
	Mean (± SD)	29.1 (6.52)
Age Category: N (%)	18 - 25	12 (30.8)
	26 - 30	11 (28.2)
	31 - 35	5 (12.8)
	>35	11 (28.2)
Gender: N (%)	Male	24 (61.5)
	Female	15 (38.5)
Ethic Origin: N (%)	Black	26 (66.7)
	Caucasian	9 (23.1)
	Hispanic	3 (7.7)
	Amerasian	1 (2.6)
Height (cm)	N	39
	Mean (± SD)	175.3 (8.35)
	Median	175
	Minimum	158
	Maximum	191
Weight (kg)	N	39
	Mean (± SD)	72.65 (11.09)
	Median	72.0
	Minimum	53.9
	Maximum	97.7

SD = standard deviation

Study Design:

This was a randomized, double-blind, double-dummy, Latin square, placebo-controlled, four-period, crossover trial evaluating the dose proportionality — of oral — 80 mg, 120 mg, and 160 mg capsules in healthy male and female subjects. After obtaining informed consent, 36 healthy subjects were randomly assigned to 1 of the 24 possible sequences of the 4 treatments. At least one subject was randomly assigned to each sequence.

Following a 4-hr fasting period, subjects received, as a single oral dose, the dose of — or placebo of their randomly assigned sequence for the dosing period between 9:30-10:30 PM. There was a minimum of 7 days between each dose of — or placebo. The expected duration of the study was approximately 26 days.

Study Drugs:

The following test drug doses were used in this clinical trial:

- — 80 mg capsules, lot #PF261 EA991 — 120 mg capsules, lot #PF262EA988 160 mg capsules, lot #PF263EA989

- Placebo 80 mg capsules, lot #PF250EA960 Placebo 120 mg capsules, lot #PF248EA958 Placebo 160 mg capsules, lot # PF272EA990

Collection of Samples:

Blood samples (approximately 7 ml) for plasma levels of total propranolol (conjugated and unconjugated) were collected pre-dose and at the following post-dose time points: 2.0-hr, 4.0-hr, 4.5-hr, 6.0-hr, 8.0-hr, 10.0-hr, 11.0-hr, 12.0-hr, 14.0-hr, 16.0-hr, 18.0-hr, 20.0-hr, 22.0-hr, 24.0-hr, 48.0-hr, and 72.0-hr for all the subjects at their randomized sequence.

Bioanalytical Method:

— performed the analyses for concentrations of total propranolol (conjugated and unconjugated) on the plasma samples collected using a validated — — method. The lower limit of quantitation was — ng/mL.

DATA ANALYSIS:

- ***Safety:*** Safety assessments including hematology tests, blood chemistry assays, urinalysis, physical examinations, ECG, and vital signs were performed at screening and study termination. Vital signs were also recorded over a 72-hr period following study drug administration during each dosing period. The monitoring and recording of all AEs occurred throughout the study.

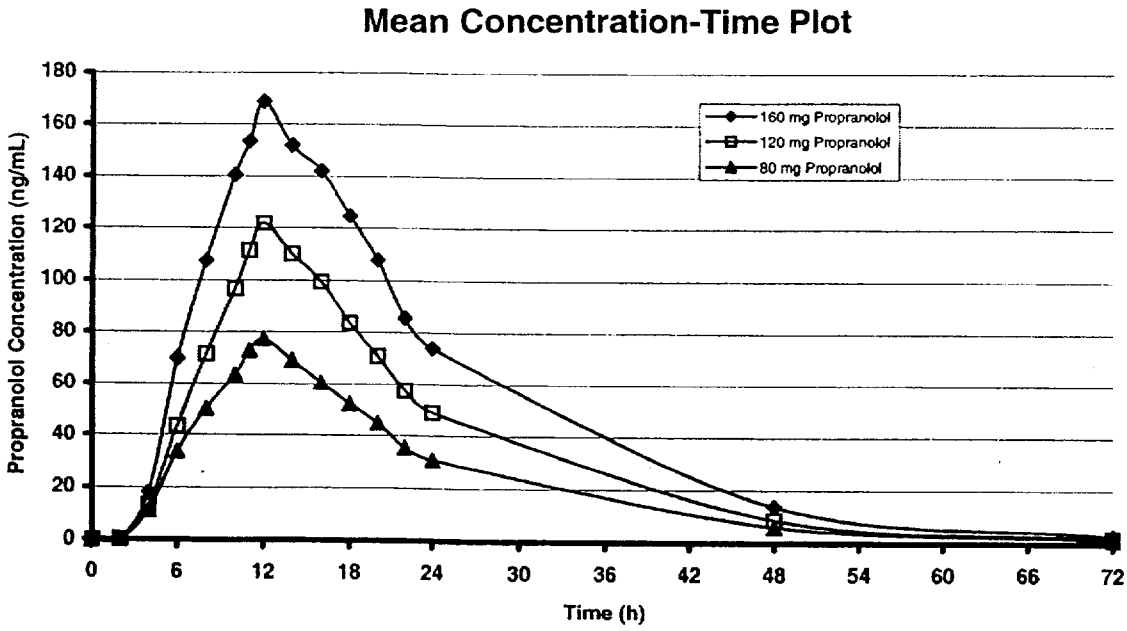
-

- ***Pharmacokinetics:*** The following parameters were derived from the plasma data: the maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), terminal elimination half-life (T1/2), area under the plasma concentration-time curve to the last measurable time point (AUC0-t), total area under the plasma concentration-time curve to infinity time (AUC0-inf), and absorption lag time (Tlag).

  Descriptive statistics and graphic presentations were used to examine the plasma level concentration profile over time for each dose. Regression analysis and analysis of variance (ANOVA) were employed for the assessment of dose proportionality. ANOVAs of the normalized and log-transformed pharmacokinetic parameters AUC0-t, AUC0-inf, and Cmax were utilized to test the differences in PK parameter values between each of the two high doses (120 mg and 160 mg) and the low dose (80 mg). The test consisted of constructing 90% confidence intervals for the ratios 120 mg/80 mg and 160 mg/80 mg, using adjusted means and their standard errors from the ANOVAs. The adjusted mean, lower and upper confidence limits were transformed back to the arithmetic scale. Each analysis of variance model included effects for period, subject (sequence), and dose.

RESULTS:

- ***Pharmacokinetics:*** The next Figure illustrates propranolol mean (SD) concentrations versus time.



A summary of the pharmacokinetic parameters and an analysis of variance to assess dose proportionality on of AUC0-t, AUC0-inf, Cmax, T1/2, and Tlag are presented in the next table.

Summary of Mean (SD) Pharmacokinetic Parameters and Statistics for —— (n=36)

PHARMACOKINETICS				STATISTICS				
Parameter	Mean (SD)			Normalized Adjusted Mean			Ratio & 90% CI	
Parameter	80 mg	120 mg	160 mg	80 mg	120 mg	160 mg	120/80 mg	160/80 mg
*AUC_{0-t} (ng.h/ml)	1443 (844)	2270 (1231)	3417 (2047)	14.6	15.4	17.4	1.1 96-116%	1.2 108-131%
*AUC_{0-inf} (ng.h/ml)	1569 (865)	2413 (1287)	3589 (2081)	16.1	16.5	18.5	1.0 94-112%	1.1 105-125%
*C_{max} (ng/ml)	80.5 (31.5)	130 (52.3)	177 (70.6)	0.9	1.0	1.0	1.1 98-116%	1.1 102-121%
T_{max} (hour)	9.5 (5.1)	8.5 (4.7)	9.1 (4.4)	-	--	-	-	-
T_{lag} (hour)	12.2 (1.9)	12.8 (2.5)	12.8 (2.7)	-	-	-	-	-
$T_{1/2}$ (hour)	2.2 (1.1)	2.1 (0.89)	1.9 (0.67)	-	-	-	-	-

*Adjusted mean and 90% CI calculated from ANOVA on normalized, log-transformed data.
Adjusted means and CIs displayed have been transformed from log to arithmetic scale

The adjusted means for pharmacokinetic parameters AUC0-t, AUC0-inf, and Cmax, showed dose proportional increases following single dose administration of 80 mg, 120 mg, and 160 mg, —— The absorption lag time (Tlag) and time to maximum drug concentration (Tmax) were similar across all —— dose groups. After Hour 12, plasma propranolol concentrations decreased at a consistent and similar rate in all —— dose groups. The mean ratios of dose-normalized AUC and Cmax were 1.0 or 1.1, indicating dose proportionality.

Safety: No deaths or serious adverse events occurred during this study. Twenty-seven treatment-emergent adverse events were reported by 11 subjects (28.2%) during this study, none of which were described as serious or severe by the investigator. Four subjects (10.2%) experienced adverse events that were considered possibly related to study drug by the investigator. One subject (2.6%) was noted to have clinically significant increases in LDH, SGOT, SGPT, and creatine kinase, one subject (2.6%) experienced nausea following the administration of placebo, one subject (2.6%) experience nausea and vomiting following —— 120 mg, and one subject (2.6%) reported headache after receiving —— 80 mg dose.

Maximal mean decreases in systolic blood pressure occurred at 8 to 10 hours post-dose in all groups,

and maximum decreases in diastolic blood pressure were observed at 8 hours post-dose in the —— 120 mg and placebo groups and 14 hours post-dose following —— 80 mg and 160 mg. No subject experienced postural hypotension during the study.

REVIEWER COMMENTS:

1. *With respect to the bioassay for propranolol, the provided assay validation information and Quality Control data are appropriate and acceptable.*
2. *The overall results of the study indicate that —— AUC and Cmax are dose proportional in the dose range of 80 to 160 mg.*

APPEARS THIS WAY
ON ORIGINAL

Study Report Summary

Study No. 3002

Study Title: A Randomized, Open-Label, Two-Period Cross-Over Study to Assess the Effect of Food on ——— Bioavailability in Healthy, Adult Subjects.

Principal Investigator/Investigation Site:
William Smith, MD/ New Orleans Center for Clinical Research, New Orleans, LA

Objective:
The primary objective of this two-period cross-over study was to assess the effect of concomitant food intake on the bioavailability of ——— in healthy subjects.

Study Population:
Healthy male and female between 18 and 40 years of age were enrolled in the study. Thirty-five subjects were included in the pharmacokinetic analysis and Thirty-seven in the safety analysis. Demographic data for all subjects are presented below:

Parameter	Statistic	(N = 37)
Age (years)	N	37
	Mean	27.7
	SD	5.68
	Median	26
	Minimum	18
	Maximum	40
Age Category: N (%)	18 - 24	16 (43.2)
	25 - 30	9 (24.3)
	31 - 34	9 (24.3)
	≥ 35	3 (8.1)
Gender: N (%)	Male	21 (56.8)
	Female	16 (43.2)
Ethic Origin: N (%)	black	33 (89.2)
	Caucasian	4 (10.8)
Height (cm)	N	37
	Mean	172
	SD	8.71
	Median	173
	Minimum	150
	Maximum	185
Weight (kg)	N	37
	Mean	71.57
	SD	11.14
	Median	70.6
	Minimum	52.0
	Maximum	96.4

SD = Standard deviation

Study Design:

This was a randomized, unblinded, single-center, two-period, cross-over study in healthy subjects evaluating the effect of food on the bioavailability of propranolol after administration of 640 mg of oral — given as four 160 mg — capsules. Eighteen subjects were randomly assigned to each sequence. Subjects received 4 capsules of 160 mg — to achieve a 640 mg dose under fasting conditions or together with a standard high-fat meal according to their assigned sequence. There was an assessment period of 3 days after each dose and a minimum period of 7 days between doses. The total duration of the study was 11 days for each subject.

Meals:

For subjects assigned to the fasting sequence, lunch was given at about 11:00 AM, after which no food was administered until 4 hours after administration of — For subjects assigned to receive food, lunch was given at about 11:00 AM, after which no food was administered until a standard high-fat meal was given beginning at 9:30 PM. The high fat meal was consumed in its entirety within 30 minutes, and — was given within no more than 1 minute after completion of the meal. A bedtime snack was offered 4 hours after dosing. Water was allowed ad libidum throughout the study for both fasting and non-fasting subjects except for 4 hours prior to and 2 hours post drug administration.

STANDARIZED HIGH-FAT MEAL

		Approximate Nutrient Content		
	Kcal	Fat (g)	Protein (g)	Carbohydrates (g)
one buttered (1 pat) English muffin (toasted)	164	5	4	25
one fried egg (in margarine)	92	7	6	1
one slice American cheese	106	9	6	0
one slice Canadian bacon	43	2	5	0
one serving (1 cup) hash browns	340	18	5	44
8 oz (240 mL) whole milk	150	8	8	11
8 oz (240 mL) apple juice	116	0	0	29
Totals	1011	49	34	110

Collection of Samples:

Blood samples (approximately 7 ml) for plasma levels of total propranolol (conjugated and unconjugated) were collected pre-dose and at the following post-dose time points: 1.0-hr, 2.0-hr, 3.0-hr, 3.5-hr, 4.0-hr, 4.5-hr, 5.0-hr, 5.5-hr, 6.0-hr, 7.0-hr, 8.0-hr, 9.0-hr, 10.0-hr, 11.0-hr, 12.0-hr, 13.0-hr, 14.0-hr, 16.0-hr, 18.0-hr, 20.0-hr, 22.0-hr, 24.0-hr, 36.0-hr, 48.0-hr, and 72.0-hr for all the subjects at each sequence.

Bioanalytical Method:

— performed the analyses for concentrations of total propranolol (conjugated and unconjugated) on the plasma samples collected using a — — . The lower limit of quantitation was — ng/mL.

□

DATA ANALYSIS:

- ***Safety:*** Safety assessments including hematology tests, blood chemistry assays, urinalysis, physical examinations, ECG, and vital signs were performed at screening and study termination. Vital signs were also recorded over a 72 hour period following study drug administration during each dosing period. The monitoring and recording of all AEs occurred throughout the study. The safety analyses focused on the frequency of AEs and on the number of laboratory values that fell outside of normal reference ranges.

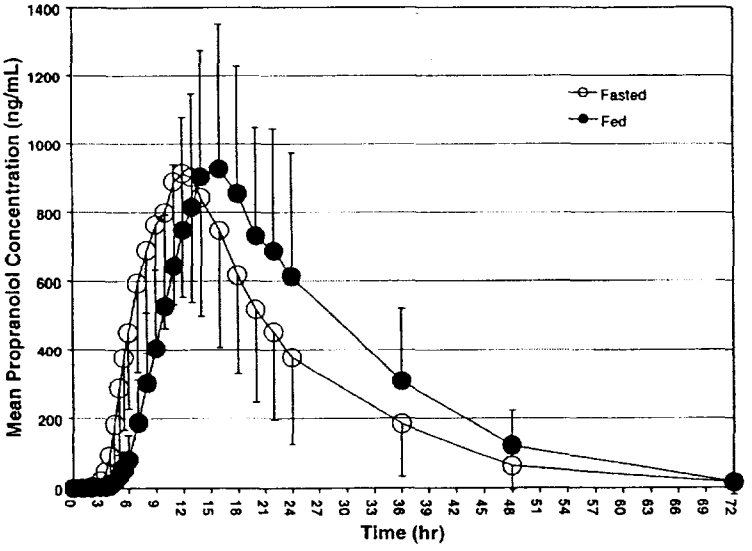
- ***Pharmacokinetics:*** The following parameters were derived from the plasma data: the maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), terminal elimination half-life (T1/2), area under the plasma concentration-time curve to the last measurable time point (AUC0-t), total area under the plasma concentration-time curve to infinity time (AUC0-inf), and absorption lag time (Tlag).

  Analysis of variance (ANOVA) on log-transformed AUC0-t, AUC0-inf, and Cmax values with subject, period, sequence, and treatment as fixed effects was performed. Adjusted means and CIs calculated by ANOVA were transformed back log to the arithmetic scale. If the 90% CI for the ratios of population geometric means (based on log-transformed data) of fed and fasted treatments fell within 80% to 125% for AUC and 70% to 143% for Cmax, then the presence of a food effect was excluded. If the CI for AUC and Cmax fell outside the above limits, then a food effect was assumed.

RESULTS:

- ***Pharmacokinetics:*** The next Figure illustrates propranolol mean (SD) concentrations versus time.

Mean (SD) Concentration-Time Profile of a Single 640 mg dose of [redacted]



Plasma concentrations of propranolol rose more rapidly in the fasted group than in the fed group with the earliest detectable difference at 2-hr post-dose (Fasted, 5 ng/mL; Fed, 0.8 ng/mL). Peak plasma propranolol concentrations (Fasted, 1003.2 ng/mL; Fed 1016.9 ng/mL) for the Fasted and Fed treatment groups were observed 11.5 hours and 15.4 hours post-dose, respectively. The Tlag was approximately 1.3 hours longer in the Fed group (2.3 hours) compared with the Fasted group (1.0 hour). Between 16

and 48 hour post-dose plasma concentrations of propranolol decreased more rapidly in the fasted group (747.3 ng/mL to 64.1 ng/mL) compared within the fed group (926.6 ng/mL to 122.2 ng/mL). At 72-hr post-dose, plasma propranolol concentrations were comparable between the two treatment groups (Fasted, 16.0 ng/mL; Fed 17.4 ng/mL).

A summary of the pharmacokinetic parameters and statistical analysis is presented in the next table. As shown, mean maximum plasma levels of propranolol (Tmax) were observed at 11.5 hours and 15.4 hours post-dose for the subjects in the Fasted and Fed treatment groups, respectively. However, a high fat meal did not affect the half-life.

Summary of Mean (SD) Pharmacokinetic Parameters and Statistics for —— 640 mg (n=35)

PHARMACOKINETICS			STATISTICS			
Parameter	**Fasted**	**Fed**	**Adjusted Mean Fasted***	**Adjusted Mean Fed***	**Ratio**	**90% CI**
AUC_{0-t} (ng.h/ml)	18584.8 (9031)	21825 (10617)	16295	19363	1.2	106-133%
AUC_{0-inf} (ng.h/ml)	18975 (9593)	22179 (10869)	16536	19661	1.2	106-133%
C_{max} (ng/ml)	1003 (344)	1017 (431)	936	930	1	89-111%
T_{max} (hour)	11.5 (2.8)	15.4 (3.2)	-	-	-	-
$T_{1/2}$ (hour)	8.4 (3.5)	8.2 (2.7)	-	-	-	-
$*T_{lag}$ (hour)	1.0 (0.54)	2.3 (1.2)	-	-	-	-

*Adjusted means and CIs displayed have been transformed from log to arithmetic scale

- ***Safety:***

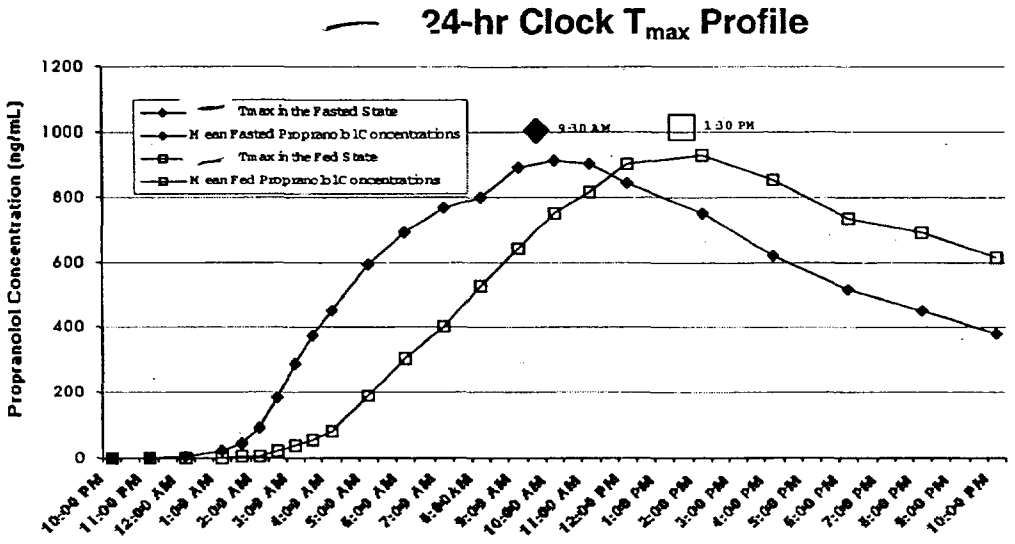
No deaths or SAEs occurred during this study. Of the 37 subjects in this study,10 (27%) reported at least one AE. The most common AEs were mild or moderate headache, nausea, and dizziness. One subject experienced severe nausea and vomiting which were not considered to be related to the study medication, but did lead to discontinuation from the study. Another subject experienced severe fatigue and weakness that were considered to be related to the study medication.

There were no significant mean changes in hematology laboratory values from screening to termination. Mean changes >10% occurred for the following serum chemistry parameters: BUN, creatine phosphokinase, LDH, phosphorus/phosphate, SGPT, total bilirubin, and uric acid. Mean decreases in systolic and diastolic blood pressure never fell below the normal limit for acceptable blood pressure (100/50 mmHg). Mean changes in heart rate were minor and were consistent with the observed effects on blood pressure.

CONCLUSIONS:

- A high fat meal affected the rate of absorption and significantly increased the bioavailability of —— There was approximate a 4 hour delay in peak plasma concentrations in the Fed group (approximately 1.3 hours longer that the Fasted group) and the 90% CI on the adjusted mean ratio of the AUCs (106-133%) were outside the acceptable range of 80% to 125%. However, propranolol Cmax concentrations were not affected by food (90% CI 89-111%).

- As illustrated in the next figure, despite the increased lag time in the fed condition, plasma propranolol concentrations increased during the morning hours to concentrations that would be considered acceptable for a therapeutic effect.



- From the safety viewpoint, was well tolerated during the study.

REVIEWER COMMENTS:

1. *With respect to the bioassay for propranolol, the provided assay validation information and Quality Control data are appropriate and acceptable.*
2. *It should be noted that for the analysis of the data, the sponsor did not follow exactly the recommendations given in the food-effect guidance. For example, the guidance recommends geometric means instead of arithmetic means, and recommends that both AUC and Cmax be within the 80-125% CI (sponsor proposal is 80-125% for AUC and 70-143% for Cmax).*
3. *Although the statistical results showed that food affects the bioavailability of , this reviewer considers that there is an absorption-time-lag effect but not a dose-dumping effect with food. Therefore, from the clinical viewpoint, food may or may not have a relevant effect on the therapeutics of this product.*

Study Report Summary

Study No. 3003

Study Title: A Randomized, Double-blind, Parallel, Placebo-Controlled, Multicenter Trial to Study the Efficacy, Safety, and Steady State Pharmacokinetics of [redacted] · Dose Levels: 80 mg, 120 mg, 160 mg, and 640 mg in Patients with Essential Hypertension

Investigator(s)/ Study Center(s): Forty-one principal investigators enrolled subjects in this study/ Multicenter study, subjects were enrolled at 41 centers in the USA.

Objectives:

- The primary objective of this double-blind study was to assess the efficacy of [redacted] treatment in subjects with essential hypertension by evaluating the mean change from Baseline to Week 8 in morning sitting diastolic blood pressure.
- The secondary objectives of this study were: 1) to assess the safety of [redacted] by recording adverse events (AEs), electrocardiogram (ECG), and laboratory measurements; 2) to determine the effect of treatment on the change from Baseline to Week 8 in mean sitting systolic blood pressure, pulse rate, and mean sitting blood pressure-rate product (mean sitting systolic blood pressure multiplied by the pulse rate) measured in the morning and evening, and mean sitting diastolic blood pressure measured in the evening; and 3) to evaluate the dose-blood level relationships and the pharmacokinetics of trough total propranolol plasma samples collected from a subgroup of subjects at Weeks 4 and 8 in each [redacted] dose group.

Patient Population:

420 planned/434 analyzed, 336 planned/427 analyzed in the ITT population, 420 in the Efficacy Evaluable population and 434 in the Safety population. Subjects were male or female outpatients who were 18 years of age or older and who had a clinical diagnosis of essential hypertension. These subjects 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.

A total of 104 subjects were in the Pharmacokinetic population. The demographic characteristics for the Pharmacokinetic population were similar to those of the Intent-to-Treat population with the exception of ethnic origin across all treatment groups and duration of hypertension in the 160 mg [redacted] dose group. There was a greater percentage of Caucasian subjects in the Pharmacokinetic population (72% to 95% across treatment groups) than in the Intent-to-Treat population (59% to 72% across treatment groups). For duration of hypertension in the 160 mg [redacted] dose group, 52.4% of the subjects had hypertension for =1 to 4 years in the Pharmacokinetic population versus 28.6% in the Intent-to-Treat population and 38.1% of the subjects had hypertension for 5 years in the Pharmacokinetic population versus 65.5% in the Intent-to-Treat population.

Demographic Characteristics - Pharmacokinetic Population

Parameter	Placebo N = 22	80 mg N = 18	120 mg N = 20	160 mg N = 21	640 mg N = 23
Age (yrs)					
N	22	18	20	21	23
Mean ± SD	53.7 ± 9.33	54.5 ± 9.92	51.3 ± 11.05	54.2 ± 11.85	53.0 ± 12.54
Age (n, %)					
18-24	0	0	0	0	0
25-29	0	0	1 (5.0)	0	0
30-49	8 (36.4)	6 (33.3)	8 (40.0)	8 (38.1)	11 (47.8)
50-64	12 (54.5)	9 (50.0)	9 (45.0)	8 (38.1)	7 (30.4)
≥65	2 (9.1)	3 (16.7)	2 (10.0)	5 (23.8)	5 (21.7)
Gender (n, %)					
Male	10 (45.5)	12 (66.7)	9 (45.0)	13 (61.9)	13 (56.5)
Female	12 (54.5)	6 (33.3)	11 (55.0)	8 (38.1)	10 (43.5)
Ethnic Origin (n, %)					
Asian	0	0	0	0	0
Black	3 (13.6)	4 (22.2)	4 (20.0)	1 (4.8)	4 (17.4)
Caucasian	19 (86.4)	13 (72.2)	16 (80.0)	20 (95.2)	18 (78.3)
Hispanic	0	1 (5.6)	0	0	1 (4.3)
Other	0	0	0	0	0
Height (in)					
N	22	18	20	21	23
Mean ± SD	66.7 ± 3.72	67.9 ± 4.90	66.9 ± 4.66	68.3 ± 3.17	68.3 ± 4.29
Weight (kg)					
N	22	18	20	21	23
Mean ± SD	85.79 ± 14.239	94.07 ± 19.112	96.86 ± 22.113	87.45 ± 14.872	95.57 ± 24.865
Duration of Hypertension (yrs)					
N	21	18	20	20	23
Mean ± SD	11.9 ± 11.691	8.9 ± 7.518	9.1 ± 8.366	7.1 ± 8.666	8.8 ± 8.643
Duration of Hypertension (n,%)					
<1 yr	1 (4.5)	1 (5.6)	1 (5.0)	1 (4.8)	2 (8.7)
≥1 to 4 yrs	8 (36.4)	5 (27.8)	6 (30.0)	11 (52.4)	9 (39.1)
≥5 yrs	12 (54.5)	12 (66.7)	13 (65.0)	8 (38.1)	12 (52.2)
Unknown	1 (4.5)	0	0	1 (4.8)	0

SD = standard deviation.

Study Design:

This was a randomized, double-blind, parallel, placebo-controlled, multicenter trial comparing the efficacy, safety, and pharmacokinetics of oral — 80 mg, 120 mg, 160 mg, and 640 mg (given as four 160 mg — capsules) once daily with placebo in subjects with essential hypertension. Matching placebo capsules identical in size, shape, and color to the 3 active strengths of — capsules were used to maintain the blind. After signing consent, all subjects were evaluated during a 2- to 3-week single-blind placebo run-in phase. Before enrolling subjects in the study, antihypertensive medication was withdrawn

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according to manufacturers' recommendations and standard practice. Diastolic and systolic blood pressure assessments were made and subjects with a mean sitting resting diastolic blood pressure within the range of 96 mm Hg to 114 mm Hg and a mean sitting resting systolic blood pressure =200 mm Hg at 2 consecutive weekly visits qualified for randomization. Subjects were randomized to one of the following five double-blind treatment groups: placebo, —— 80 mg/day, —— 120 mg/day, —— 160 mg/day, or —— 640 mg/day taken once nightly between 9:30 to 10:30 PM. During Week 1 and Week 2, subjects were up titrated to the appropriate dose. Subjects remained at a stable dose for 6 weeks, and then they were down titrated for the last two weeks of the study. Subjects randomized to receive placebo and —— 80 mg received their respective treatments throughout the study.

Treatment Schedule & Duration of Treatment:

The treatment schedule is presented in the next table.

	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).

Subjects received up to three weeks of placebo once daily during the placebo run-in phase followed by 10 weeks (once daily, including up titration and down titration in the 120 mg, 160 mg, and 640 mg groups) of either placebo, 80 mg, 120 mg, 160 mg, or 640 mg of

Study Medications:

- ***Test Product:*** —— 80 mg, 120 mg, 160 mg, and 640 mg extended release capsules
  Active 80 mg capsules, lot # PF261EA991; Active 120 mg capsules, lot # PF262EA988; and Active 160 mg capsules, lot # PF263EA989

- ***Reference Therapy:*** placebo capsules identical in appearance to —— capsules
  Placebo 80 mg capsules, lot # PF250EA960; Placebo 120 mg capsules, lot # PF248EA958 and lot # PF248EA001; Placebo 160 mg capsules, lot # PF272EA990

DATA ANALYSIS:

- ***Primary Efficacy Parameter:*** The primary efficacy parameter of this study was the mean change from Baseline to Week 8 in sitting diastolic blood pressure taken in the morning.
- ***Secondary Efficacy Parameters:*** The secondary efficacy parameters of this study were the mean change from Baseline to Week 8 in sitting systolic blood pressure, pulse rate, and sitting systolic blood pressure-rate product (systolic blood pressure multiplied by the pulse rate) measured in the morning and at trough propranolol level (approximately 4 hours prior to next dosing), and diastolic blood pressure measured at trough propranolol level.

- ***Safety & Tolerability:*** Safety and tolerability were assessed by evaluating AEs, laboratory values, physical examinations, electrocardiograms (ECGs), and vital signs.

- ***Pharmacokinetics:*** Drug concentration and pharmacokinetic evaluation were assessed in a subgroup of subjects from selected sites. The primary objective of this subgroup analysis was to determine trough propranolol levels and to evaluate pharmacokinetics in a subgroup of subjects from 5 to 10 randomly selected sites from the sites participating in this study. Sixty subjects were planned and 104 subjects from 8 sites (sites 7, 11, 14, 19, 23, 32, 39, and 41) actually comprised the PK population. Mean of Weeks 4 and 8 trough plasma propranolol levels were analyzed.

- ***Bioanalytical Determinations:*** performed the analyses for concentrations of total propranolol (conjugated and unconjugated) on the plasma samples collected using a validated method. The lower limit of quantitation was — ng/mL.

STATISTICS:

Unless otherwise specified, all statistical tests were conducted against a 2-sided alternative hypothesis at the 0.05 level of significance.

- ***Efficacy:***
  Primary Analyses: Change from Baseline to Endpoint in morning mean sitting diastolic blood pressure was analyzed for differences among the dose groups using analysis of covariance (ANCOVA) with treatment and center as factors and the Baseline mean sitting diastolic blood pressure as a covariate.
  Secondary Analyses: The secondary efficacy variables were analyzed and summarized similarly as described above for the primary efficacy variable.

- ***Pharmacokinetic Analysis:*** Summary statistics (N, mean, median, standard deviation, minimum and maximum) on the original scale were presented in tabular form for the Week 4, Week 8, and overall mean trough propranolol levels. A mixed-model analysis of variance was used to test for a difference between Week 4 and Week 8 trough propranolol levels. The primary objective was tested using regression on mean trough level on dose. Multivariate methods were used to examine the relationship between mean trough plasma total propranolol levels and the primary and secondary efficacy parameters. Similar methods were used to explore the relationship of subject characteristics to mean trough levels.

  The relationship between trough propranolol levels and Baseline subject characteristics such as Baseline diastolic blood pressure, age, gender, and ethnic origin as well as study-related factors such as percent subject compliance to the study treatment regimen was also examined. For the subject characteristics that were related to trough propranolol levels, the interaction with dose level was assessed.

- **Other Analyses:** Summary statistics were presented for background and demographic characteristics for all subjects. Continuous variables were summarized by sample size, mean, median, standard deviation, minimum, and maximum. Treatment groups were compared using analysis of variance (ANOVA) with treatment and center as factors. Discrete variables were summarized by frequencies (or

numbers) and percentages and the treatment groups were compared using the Cochran-Mantel-Haenszel test with center as the stratification variable. The safety analyses focused on the frequency of AEs and the number of laboratory values that fell outside of normal reference ranges. Other safety data (e.g., ECG, vital signs) were considered as appropriate.

RESULTS:

- ***Primary Efficacy:*** Morning sitting diastolic blood pressure decreased from Baseline to Endpoint for the placebo and all four — groups. Statistically significant differences in the magnitude of the decrease between the placebo group and the 120 mg, 160 mg, and 640 mg — groups were observed for the primary analysis in both the Intent-to-Treat population and the Efficacy Evaluable population. Statistical trends were observed for the 80 mg — dose group in both populations.

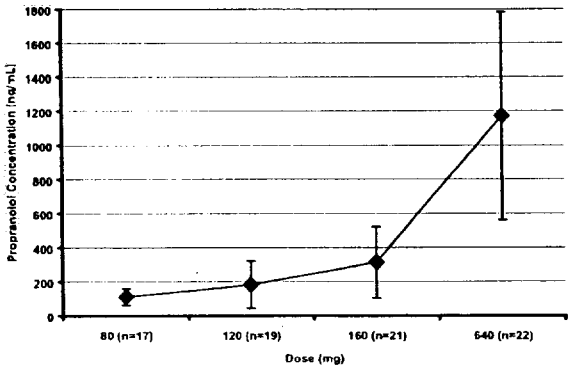
- ***Secondary Efficacy:*** Evening sitting diastolic blood pressure also decreased from Baseline to Endpoint for the placebo and all four — groups. The decrease in evening diastolic blood pressure in the groups was significantly greater than the decrease in the placebo group for the Intent-to-Treat and Efficacy Evaluable populations for the primary (LOCF) analysis.
  A decrease from Baseline to Endpoint was observed for both morning and evening systolic blood pressure in all treatment groups. Statistically significant differences in the magnitude of the decrease between the placebo group and the groups were observed for evening systolic blood pressure at the 80 mg and 640 mg — doses for the primary (LOCF) analysis.
  Decreases from Baseline to Endpoint were also observed for morning and evening pulse rate and morning and evening BPRP in all treatment groups and statistical analyses revealed a statistically greater decrease in all — dose groups than in the placebo group for these parameters for the primary (LOCF) analysis.
  Box plots of the distribution of change from baseline in efficacy parameters according to treatment group within centers showed no consistent evidence of a treatment by center effect. In general, the primary and secondary efficacy results in subject subgroups by age, gender, ethnic origin, and duration of hypertension were similar to those of Intent-to-Treat population.

- ***Safety:*** Approximately half of the 434 subjects in the safety population experienced at least one AE during double-blind treatment in this study. The most commonly reported AEs (>5% in any treated group) were headache, fatigue, dizziness (excluding vertigo), and insomnia. Approximately 95% of AEs in — -treated subjects were classified as mild or moderate and approximately 40% of AEs in — -treated subjects were deemed by the investigator to be related to study drug. There did not appear to be any clinically relevant difference in AEs reported by age group, gender, ethnic origin, or duration of hypertension. A total of 26 subjects discontinued due to an AE (Total — 5.8%; Placebo 6.8%) during the double-blind treatment phase of the study. The 640 mg — group had more subjects that discontinued due to an AE (11.5%) than the other — dose groups (1% to 7%). No deaths occurred during this study. Four subjects experienced SAEs during the double- blind treatment phase of this study. Three of the four subjects were in a dose group and 1 subject was in the placebo group. One — treated subject experienced an SAE 7 days after completing the study. No clinically significant changes occurred in hematology and chemistry laboratory values, physical examination findings, or ECG findings for the subjects in this study.

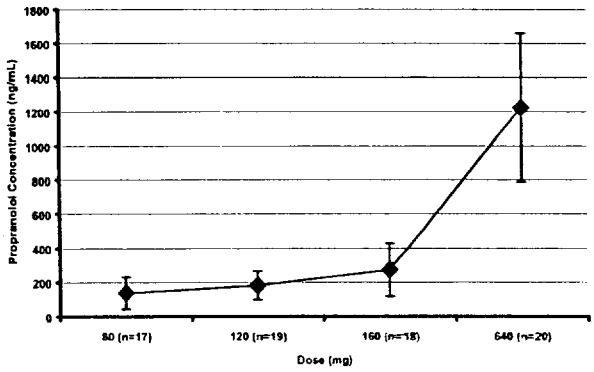
- ***Pharmacokinetics & Pharmacodynamics:***

Trough plasma propranolol levels increased in a dose-dependent manner with the administration of increasing doses at both Week 4 and Week 8. Mean trough plasma propranolol concentrations for each dose groups Weeks are presented in the next table and illustrated in the

Week 4 Dose Versus Mean Trough Propranolol Concentrations



Week 8 Dose Versus Mean Trough Propranolol Concentrations

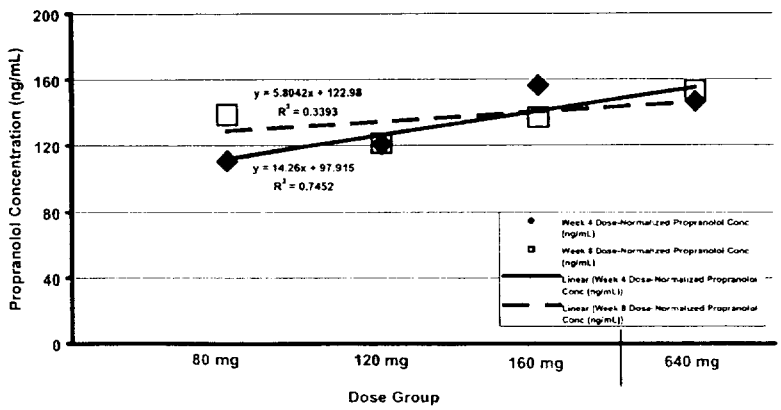


graphics.

TIME	PLACEBO	80 MG	120 MG	160 MG	640 MG
Week 4					
N	21	17	19	21	22
Mean (SD)	0.0 (0.0)	111 (49)	181 (137)	313 (210)	1172 (610)
Minimum-Maximum					
Week 8					
N	17	17	19	18	20
Mean (SD)	0.0 (0.0)	139 (93)	182 (84)	274 (155)	1224 (437)
Minimum-Maximum					
Overall Mean					
N	21	18	20	21	23
Mean (SD)	0.0 (0.0)	127 (64)	183 (103)	295 (165)	1171 (496)
Minimum-Maximum					

Following dose normalization, doses of 80, 120, 160, and 640 mg were relatively proportional at 4 and 8 weeks in this hypertensive population.

Normalized Mean Trough Propranolol Concentrations



Additional analyses were performed to evaluate the pharmacodynamic relationship between mean trough total propranolol levels and the efficacy parameters and to further evaluate the differences in trough plasma total propranolol levels between dose groups. The results showed that trough plasma propranolol levels increased in a dose-dependent manner with the administration of increasing doses at both Week 4 and Week 8. There were significant differences among the treatment groups in mean trough total propranolol levels. The inter-subject and intra-subject standard deviation estimates were 26.3 ng/mL and 24.3 ng/mL, respectively. There was no significant difference in the mean change from Week 4 to Week 8 among treatment groups, suggesting that there was no change in subject compliance or in the pharmacokinetics of total plasma propranolol during the course of treatment, even at the 640 mg dose.

Pharmacodynamic analysis of efficacy parameters showed statistically significant correlations between trough total propranolol level and change from Baseline to Endpoint in evening diastolic blood pressure ($p=0.0263$), morning pulse rate ($p\leq 0.0001$), evening pulse rate ($p=0.0013$), morning BPRP ($p\leq 0.0001$). and evening BPRP ($p=0.0039$). Regression analysis of natural log transformed trough total propranolol levels and efficacy parameters (excluding placebo subjects) indicated the same significant correlations.

Subject characteristics of age, gender, ethnicity, baseline diastolic blood pressure, and percent drug compliance during the study were included with treatment group in an ANCOVA model to assess their relationship to the natural log of trough level. Of the main effects, treatment group, age, and gender showed significant ability to predict log trough levels ($p\leq 0.0001$, $p=0.0004$, $p\leq 0.0001$, respectively). None of the ANCOVA assumptions appeared to be violated in this initial model. Dose, age, gender, and interactions of dose with both age and gender were included in a final ANCOVA. The main effects of dose, age, and gender were significant ($p\leq 0.0001$, $p=0.0059$, and $p\leq 0.0001$, respectively). None of the interactions were significant, and ANCOVA assumptions appeared to be met. Based on these results. dose, age, and gender appear to be the only demographic and Baseline effects associated with propranolol trough levels.

REVIEWER COMMENT:

1. *With respect to the bioassay for propranolol. the provided assay validation information and Quality Control data are appropriate and acceptable.*

2. *The results of this study showed that in hypertensive patients, there is dose proportionality at steady state in the studied dosing range of 80-640 mg.*

3. *It should be noted that the above PK/PD results of the association of age and gender with propranolol trough level, was not documented in the proposed labeling for*

□

Study Report Summary

Study No. 3006

Study Title: A Single and Multiple Dose, Two-Period, Cross-Over Study to Evaluate the Bioavailability and Safety of 160 mg Relative to Inderal LA 160 mg in Healthy, Adult Male subjects.

Principal Investigator/Investigation Site:

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 in healthy, adult, male subjects.

Study Population:

Healthy male between 18 and 40 years of age were enrolled in the study. Thirty-five subjects were included in the pharmacokinetic analysis and Thirty-sex in the safety analysis. Demographic data for all subjects are presented below:

Parameter	All Subjects N=36
Age (yrs)	
N	36
Mean ± SD	31.4 ± 7.78
Age (n, %)	
18-25	8 (22.2%)
25-30	9 (25.0%)
30-35	6 (16.7%)
>35	13 (36.1%)
Gender (n, %)	
Male	36 (100%)
Female	0 (0)
Ethnic Origin (n, %)	
Black	3 (8.3%)
Caucasian	15 (41.7%)
Hispanic	16 (44.4%)
Other	2 (5.6%)
Height (cm)	
N	36
Mean ± SD	177.1 ± 7.55
Weight (kg)	
N	36
Mean ± SD	77.58 ± 9.88

□

Study Design:

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 160 mg capsules in healthy, adult, male subjects. After giving informed consent, 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, randomized subjects received a single dose in the evening at approximately 10:00 PM of the study drug (' —— or Inderal® LA). Subjects received a daily dose of the assigned Period-1 drug on Days 4 to 8. On Days 1 or 16, serial blood samples for plasma propranolol determinations were collected for 72 hours. On Days 5 to 8, 24-hour (trough) blood samples were collected for plasma propranolol determinations. After 5 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. The duration of the study was 23 days.

72-Hour Assessments for Each Dose Period (Study Days 1 to 3 and 16 to 18)																
		Day 1 or 16													Day 2 or 17	Day 3 or 18
		Hours Post-Dose														
Procedures	Pre-dose	2	4	6	8	10	11	12	14	16	18	20	22	24	48	72
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event inquiry														X	X	X
Blood draw for plasma propranolol levels	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

24-Hour Assessments for Each Dose Period (Study Days 8 and 23)																
	Hours Post-Dose															
Procedures	Pre-dose	1	2	3	4	6	8	10	11	12	14	16	18	20	22	24
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trough Level Assessment	X															X
Adverse event inquiry																X
Blood draw for plasma propranolol levels		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

According to the study design outlined above, in both Study Period 1 and Study Period 2, single dose pharmacokinetic sampling was followed by multiple dose administration and sampling after 72 hours. This design allowed simultaneous evaluation of the single and multiple dose bioavailability of — 160 mg relative to Inderal® LA 160 mg.

Collection of Samples:

- During the single dose period (Study Days 1 to 3 and 16 to 18), plasma levels of propranolol were measured pre-dose and at the following post-dose time points: 2.0 hr, 4.0 hr, 6.0 hr, 8.0 hr, 10.0 hr, 11.0 hr, 12.0 hr, 14.0 hr, 16.0 hr, 18.0 hr, 20.0 hr, 22.0 hr, 24.0 hr, 48.0 hr, and 72.0 hr.
- During the multiple dose period (Study Days 4 to 8 and 19 to 23), plasma levels of propranolol were measured at steady state (Study Days 8 and 23) pre-dose and at the following post-dose time points: 1.0 hr, 2.0 hr, 3.0 hr, 4.0 hr, 6.0 hr, 8.0 hr, 10.0 hr, 11.0 hr, 12.0 hr, 14.0 hr. 16.0 hr, 18.0 hr, 20.0 hr, 22.0 hr, and 24.0 hr.

The pharmacokinetic evaluations were conducted only for the 35 subjects who had sufficient values for plasma propranolol in both dosing periods to calculate the standard pharmacokinetic parameters. Subject No. 3006-01-0017 was excluded from the pharmacokinetic analysis due to one or fewer drug levels for one entire study period.

Bioanalytical Method:

performed the analyses for concentrations of total propranolol (conjugated and unconjugated) on the plasma samples collected using a validated method. The lower limit of quantitation was ng/mL.

DATA ANALYSIS:

- ***Safety:*** Safety assessments including hematology, blood chemistry, urinalysis, physical examination, ECG, and vital signs were performed at screening and study termination. Vital signs were also recorded over the 72-hr period following single dose administration of the study drug and over the 24-hr period following multiple dosing. Monitoring and recording of all adverse events occurred throughout the study.

- ***Pharmacokinetics:*** This study investigated the bioavailability of single dose administration of 160 mg relative to single dose administration of Inderal® LA 160 mg as well as their relative bioavailabilities under multiple dose administration, Therefore, the pharmacokinetic parameters for each formulation were calculated from 72-hr assessments following a single dose and from 24-hr assessments following multiple dosing.

  The following pharmacokinetic parameters were derived from the plasma data following single dose study drug administration: AUC0-t, AUC0-inf, Cmax, Tmax, Tlag, and T1/2.

  The following pharmacokinetic parameters were derived from steady-state plasma data following multiple dose study drug administration: AUC0-τss (τ is the dosing interval), Cmaxss, Tmaxss, Cminss, Tminss, Cavgss (average conc at steady-state), Racss (steady-state accumulation ratio), and Fiss (fluctuation index at steady-state).

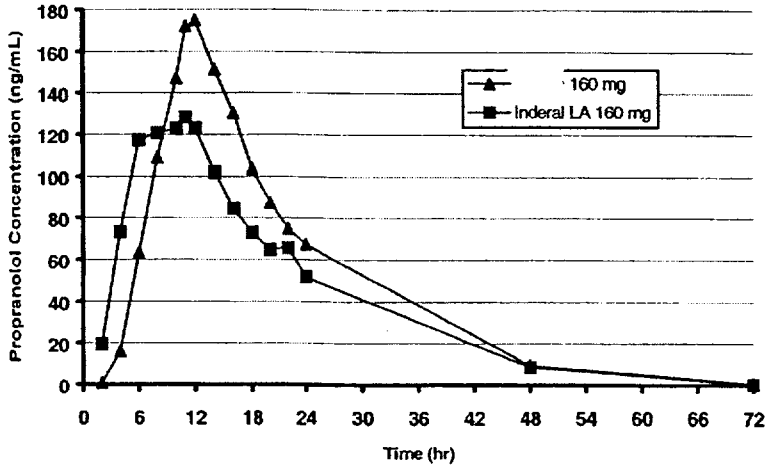
  Descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) for the single-dose PK parameters (Cmax, Tmax, Tlag, AUC0-t, AUC0-inf, tl/2) were presented in tabular form. Summary statistics and graphics were presented to compare the plasma level concentration-time profile for both formulations. Analysis of variance (ANOVA) was performed on log transformed AUC and Cmax parameters. The ANOVA model included terms for subject, period, sequence, and treatment. Adjusted means and confidence intervals for the 160 mg and Inderal® LA 160 mg treatment groups were calculated for the parameters AUC0-t, AUC0-inf, and Cmax and were transformed back to the arithmetic scale.

  The same descriptive statistics were calculated for trough levels during multiple dosing periods. The estimation of time to reach steady-state trough propranolol plasma levels was accomplished primarily by examination of the graphical displays of mean trough drug concentrations over time, but this estimation was guided by statistical testing. Analysis of variance was performed to compare the mean trough level between the 160 mg and Inderal® LA 160 mg treatment periods. Descriptive statistics were calculated for multiple-dose PK parameters (AUC0-tss, Cavgss, Racss, and Fiss). Analysis of variance was performed on log-transformed AUC0-tss in the same manner as the single-dose PK parameters.

RESULTS:

- ***Single Dose Pharmacokinetics:*** The next Figure illustrates propranolol mean concentrations versus time following a single dose administration of — 160 mg and Inderal® LA 160 mg.

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



Following a single dose of — 160 mg, there was a delayed release of propranolol for 2 to 4 hours, whereas release of propranolol following a single dose of Inderal® LA 160 mg was almost immediate. Within 3 hours after administration of Inderal® LA, mean plasma propranolol concentrations increased to approximately 50% of the mean maximum propranolol concentration. In contrast, following administration of —, 50% of the mean Cmax was not reached until approximately 7 hours post administration. Between 10 hr and 12 hr post dose (8:00 to 10:00 AM), mean plasma concentrations in the Inderal® LA group remained relatively constant (range 122.8 ng/mL to 128.2 ng/mL) while mean plasma concentrations in the — group steadily increased (range 146.9 ng/mL to 174.8 ng/mL). The time to maximum plasma levels of propranolol (Tmax) was 10.5 hr and 11.9 hr for subjects administered Inderal® LA and — respectively. The elimination half-life (t1/2) was similar for both formulations.

A summary of the single dose pharmacokinetic parameters and an ANOVA on AUC0-t, AUC0-inf, and Cmax are presented in the next Table.

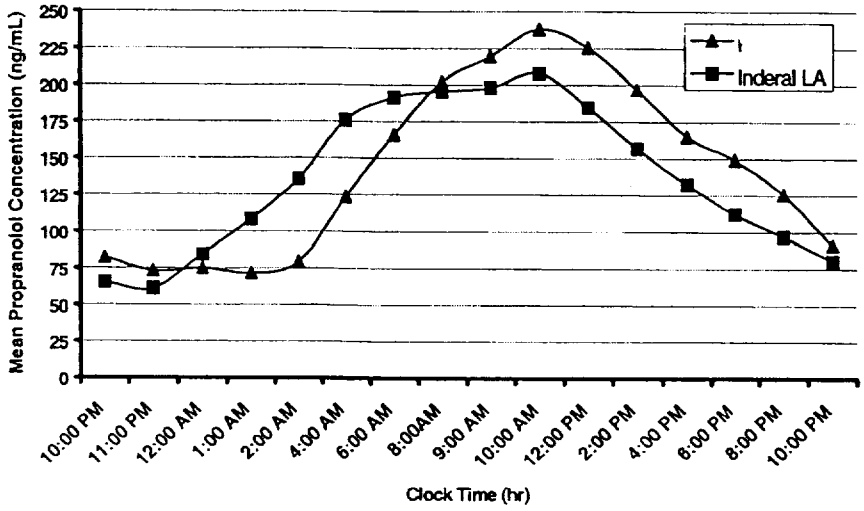
Summary of Single Dose Mean (SD) Pharmacokinetic Parameters and Statistics (n=35)

PHARMACOKINETICS			STATISTICS			
Parameter	Inderal LA 160 mg	— 160 mg	Adjusted* Inderal LA 160 mg	Adjusted* — 160 mg	Ratio	90% CI
AUC_{0-t} (ng.h/ml)	2830 (1211)	3247 (1565)	2589	2944	1.1	102-127%
AUC_{0-inf} (ng.h/ml)	2845 (1212)	3266 (1569)	2605	2963	1.1	102-127%
C_{max} (ng/ml)	149 (82)	187 (85)	131	171	1.3	112-153%
T_{max} (hour)	10.5 (4.0)	11.9 (1.9)	-	-	-	-
$T_{1/2}$ (hour)	7.9 (2.4)	7.6 (2.3)	-	-	-	-
*T_{lag} (hour)	0.2 (0.56)	2.2 (1.3)	-	-	-	-

*Adjusted means and 90%CIs calculated from ANOVA on log-transformed parameters.
Adjusted means and CIs displayed have been transformed from log to arithmetic scale

- ***Steady-State Pharmacokinetics:*** The next Figure illustrates propranolol mean concentrations versus time following multiple dose administration of — 160 mg and Inderal® LA 160 mg.

Mean Concentration-Time Profiles of — 160 mg Compared with Inderal LA 160 mg (Steady State)



Following multiple doses of — 160 mg, there was a delayed release of propranolol for 2 to 6 hrs, whereas release of propranolol for Inderal® LA a slight delay of less than 1 hr can be detected.

A summary of the steady state pharmacokinetic parameters and statistics is presented in the next table. Both formulations showed similar accumulation at steady state and propranolol concentrations fluctuated in a similar manner over the dosing interval.

Summary of Steady-State Mean (SD) Pharmacokinetic Parameters and Statistics (n=35)

PHARMACOKINETICS			STATISTICS			
Parameter	Inderal LA 160 mg	— 160 mg	Adjusted* Inderal LA 160 mg	Adjusted* — 160 mg	Ratio	90% CI
$AUC_{0\text{-}tss}$ (ng.h/ml)	3471 (1689)	3646 (1617)	3115	3326	1.1	98-116%
C_{maxss} (ng/ml)	230 (119)	248 (104)	129	138	1.1	98-117%
C_{minss} (ng/ml)	56.3 (38.2)	58.9 (37.9)	1.7	1.7	1.0	81-113%
C_{avgss} (ng/ml)	143 (69.6)	151 (66.6)	114	127	1.1	99-124%
T_{maxss} (hour)	10.9 (3.4)	12.6 (1.9)	-	-	-	-
T_{minss} (hour)	5.1 (8.7)	7.3 (8.7)	-	-	-	-
R_{acss}	1.9 (0.97)	1.8 (0.7)	-	-	-	-
F_{iss}	121 (42.6)	131 (31.4)	-	-	-	-

*Adjusted means and 90%CIs calculated from ANOVA on log-transformed parameters. Adjusted means and CIs displayed have been transformed from log to arithmetic scale

- ***Safety:***
  No deaths or serious adverse events occurred during this study. After administration of [redacted] 1 subject discontinued prematurely from the study due to adverse events (mild dizziness, bradycardia, and fatigue). Subjects experienced more adverse events during [redacted] administration than during Inderal® LA administration (27.8% of subjects vs 11.6% of subjects, respectively), but none were considered severe by the investigator. Two of 6 subjects experienced adverse events after receiving Inderal® LA 160 mg and 17 of 24 subjects experienced adverse events after receiving [redacted] 160 mg that were deemed drug-related by the investigator. No clinical laboratory values were considered adverse events in this study. There were no clinically significant changes in vital signs, physical examination findings, or ECG parameters from screening to study termination. Overall, Inderal® LA 160 mg [redacted] 160 mg was both safe and well-tolerated by subjects in this study.

CONCLUSIONS:

- Both formulations attained steady state at approximately the same time (2 days) and had similar elimination rates at acute and steady state. Also, plasma propranolol concentrations at steady-state fluctuated in a similar manner for both formulations.

- At acute and steady state phases, the [redacted] formulation demonstrated both delayed and sustained release characteristics over a duration that would cover waking hours of the morning.

- After single-dose administration of Inderal® LA 160 mg or [redacted] 160 mg, the maximal decreases in mean blood pressure occurred approximately 8 hr post dose (-6:00 AM) in both groups; the maximal decreases in mean heart rate occurred between 6 hr and 8 hr post dose (4:00 AM to 6:00 AM). After multiple dose administration, the maximal decreases in mean blood pressure occurred between 3 hr and 8 hr post dose (1:00 AM to 6:00 AM); the maximal decreases in mean heart rate occurred between 6 hr and 11 hr post dose (-4:00 AM to 9:00 AM).

- Overall, both formulations of propranolol were well tolerated during the study.

REVIEWER COMMENTS:

1. *With respect to the bioassay for propranolol, the provided assay validation information and Quality Control data are appropriate and acceptable.*
2. *The results of the study showed greater plasma propranolol concentrations for the [redacted] formulation. The relative bioavailabilities (Frel) of [redacted] vs. Inderal after single dose and at steady state were 1.5 and 1.1, respectively. There was not accumulation of propranolol after multiple dosing of the 160 mg [redacted] formulation.*

Study Report Summary

Study No. 3007

Study Title: 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.

Principal Investigator/Investigation Site:
William Smith, MD/ New Orleans, LA

Objective:
To evaluate the preliminary pharmacokinetics and safety of —— 160 mg relative to that of Inderal® LA 160 mg following single dose administration in healthy, adult, male subjects.

Study Population:
Twelve healthy male between 18 and 40 years of age were enrolled in the study. Demographic data for all subjects are presented below:

Parameter	Statistic	(N = 12)
Age (years)	N	12
	Mean	30.1
	SD	8.03
	Median	33
	Minimum	19
	Maximum	40
Age Category: N (%)	18 - 25	4 (33.3)
	25 - 30	1 (8.3)
	30 - 35	3 (25.0)
	>35	4 (33.3)
Gender: N (%)	Male	12 (100.0)
	Female	0 (0.0)
Ethic Origin: N (%)	Black	10 (83.3)
	Caucasian	2 (16.7)
Height (cm)	N	12
	Mean	179.7
	SD	11.63
	Median	179
	Minimum	155
	Maximum	196
Weight (kg)	N	12
	Mean	78.81
	SD	14.370
	Median	77.7
	Minimum	61.8
	Maximum	107.7

SD: Standard Deviation

Study Design:
This was a randomized, open-label, active-controlled, two-period, cross-over trial that evaluated the preliminary pharmacokinetics and safety of —— capsules and Inderal® LA following a single 160 mg oral administration to 12 healthy male subjects. Subjects were randomly assigned to one of the following two possible sequences. Six subjects were randomly assigned to each sequence.

□

SEQUENCE	DOSE (MG) / PERIOD	
	1	2
1	— 160	Inderal® LA
2	Inderal® LA	— 160

Six subjects per sequence

During Period 1, subjects fasted for 4 hr and then received a single oral dose of either 160 mg of — or 160 mg of Inderal® LA according to their assigned sequence. Subjects stayed in the clinical testing facility for 72 hours. Following a minimum 7-day washout interval, subjects returned to the clinical testing facility to receive the alternate study drug administration after a 4 hr fast.

This cross-over study was designed to reduce any bias due to the order of study drug administration and variability when comparing — 160 mg to Inderal® LA 160 mg with respect to bioavailability and safety. The cross-over design allowed for the assessment of relative pharmacokinetics with fewer subjects, since the within-subject variability was much less than the between-subject variability for the pharmacokinetic parameters used to measure bioavailability. The study was designed to determine the most appropriate blood collection times needed to assess the bioavailability of the new formulation of — . Based on the plasma concentration versus time curves for propranolol obtained in this study, blood collection times were to be determined for future trials.

Collection of Samples:

At each period, plasma levels of propranolol were measured pre-dose and at the following post-dose time points: 0.5 hr, 1.0 hr, 1.5 hr, 2.0 hr, 2.5 hr, 3.0 hr, 3.5 hr, 4.0 hr, 4.5 hr, 5.0 hr, 5.5 hr, 6.0 hr, 7.0 hr, 8.0 hr, 9.0 hr, 10.0 hr, 11.0 hr, 12.0 hr, 13.0 hr, 14.0 hr, 16.0 hr, 18.0 hr, 20.0 hr, 22.0 hr, 24.0 hr, 36.0 hr, 48.0 hr, and 72.0 hr.

The pharmacokinetic evaluations were conducted only for the nine subjects who had sufficient values for plasma propranolol to calculate the standard pharmacokinetic parameters. Subjects No. 01-0003, No. 01-0004, and No. 01-0020 were excluded from the pharmacokinetic analysis because they had one or fewer drug levels for one entire period during the study.

Bioanalytical Method:

— performed the analyses for concentrations of total propranolol (conjugated and unconjugated) on the plasma samples collected using a validated — method. The lower limit of quantitation was — ng/mL.

DATA ANALYSIS:

- ***Safety:*** Safety assessments including hematology, blood chemistry, urinalysis, physical examination, ECG, and vital signs were performed at screening and study termination. Vital signs were also recorded over the 72-hr period following single dose administration of the study drug and over the 24-hr period following multiple dosing. Monitoring and recording of all adverse events occurred throughout the study.

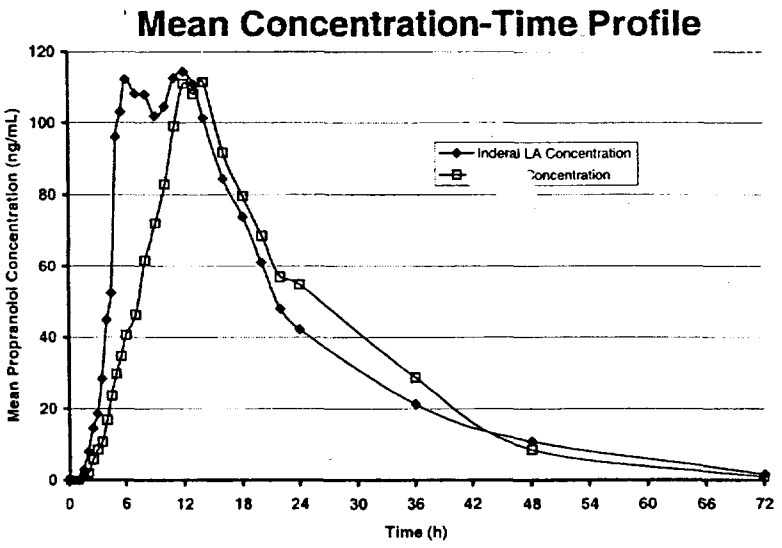
- ***Pharmacokinetics:*** To determine the preliminary pharmacokinetics of a single dose of — 160 mg as a timed-release formulation relative to a single dose of Inderal® LA 160 mg, the following parameters were derived from the plasma data: maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), terminal elimination half-life (tl/2), area under the plasma

concentration versus time (0-72) curve (AUC0-72 hr), and area under the plasma concentration curve versus infinite time (AUC0-inf).

Summary statistics (i.e., sample size, mean, median, standard deviation, minimum, and maximum) were presented for the above parameters in tabular form. Summary statistics and graphics were presented to examine the plasma level concentration profile over time for each dose. Analysis of variance (ANOVA) was performed on log transformed AUC and Cmax. The ANOVA model included terms for subject, period, carryover, and treatment. Adjusted means and confidence intervals for the —— 160 mg and Inderal® LA 160 mg treatment groups were calculated for the parameters AUC0-72 hr, AUC0-inf, and Cmax and were transformed back to the arithmetic scale.

RESULTS:

- ***Pharmacokinetics:*** The next Figure illustrates propranolol mean concentrations versus time following a single dose administration of —— 160 mg and Inderal® LA 160 mg.



A summary of the pharmacokinetic parameters and statistics on AUC0-72, AUC0-inf, and Cmax are presented in the next Table.

Summary of Single Dose Mean (SD) Pharmacokinetic Parameters and Statistics (n=9)

PHARMACOKINETICS			STATISTICS			
Parameter	Inderal LA 160 mg	—— 160 mg	Adjusted* Inderal LA 160 mg	Adjusted* —— 160 mg	Ratio	90% CI
AUC_{0-72} (ng.h/ml)	2414 (1218)	2268 (934)	2093	2042	1.0	78-122%
AUC_{0-inf} (ng.h/ml)	2565 (1331)	2332 (969)	2200	2095	1.0	56-120%
C_{max} (ng/ml)	154 (110)	121 (37.8)	128	116	0.9	61-134%
T_{max} (hour)	10.6 (3.1)	13.1 (2.4)	-	-	-	-
$T_{1/2}$ (hour)	10.1 (5.3)	7.6 (3.1)	-	-	-	-

*Adjusted means and 90%CIs calculated from ANOVA on log-transformed parameters. Adjusted means and CIs displayed have been transformed from log to arithmetic scale

The earliest time point that measurable plasma levels of propranolol were observed was 1.5 hr post-dose in both groups. Between 1.5 hr and 6.0 hr post-dose, the mean plasma concentration increased from 3.0 ng/mL to 112.3 ng/mL in the Inderal® LA group compared with 1.0 ng/mL to 40.6 ng/mL in the — group. Between 6 hr and 12 hr post-dose, plasma concentrations in the Inderal® LA group remained relatively constant (range — ng/mL to — ng/mL) while plasma concentrations in the — group steadily increased (range — ng/mL to — ng/mL). At 13 hr post-dose, the mean plasma concentrations were 110.9 ng/mL and 108.1 ng/ml in the Inderal® LA and — groups, respectively. After 14 hr post-dose, plasma concentrations decreased at a consistent and similar rate in both groups.

- ***Safety:***
  No deaths or serious adverse events occurred during this study. Two subjects experienced a total of four adverse events involving moderate to severe nasal congestion and headache of moderate severity. In the judgment of the investigator, the four adverse events were possibly related to the administration of — 160 mg.

  No clinically significant changes were noted in hematology, clinical chemistry, or urinalysis laboratory parameters. Maximal mean decreases in systolic blood pressure occurred 8 hr and 9 hr post-dose after the administration of Inderal® LA 160 mg and — 160 mg, respectively. However, maximal mean decreases in diastolic blood pressure occurred at 8 hr post-dose for both study drugs. The mean changes all remained within the normal range for this healthy population. No subject had postural hypotension during the study. Mean changes in heart rate were not clinically meaningful. The initial and final physical examinations for most subjects were normal, and all abnormalities present were due to pre-existing conditions and not considered to be relevant to the study.

CONCLUSIONS:

- The pharmacokinetic parameters of AUC and Cmax for — 160 mg were similar to those of Inderal® LA 160 mg. The adjusted mean ratio of — 160 mg/Inderal® LA 160 mg was 1.0 for AUC0-72 and AUC0-inf, and 0.9 for Cmax. The adjusted mean maximum plasma concentrations (Tmax) were 115.5 ng/mL for subjects administered — 160 mg treatment group and 128.3 ng/mL for subjects administered Inderal® LA 160 mg, respectively. However, the — 160 mg formulation resulted in a delayed release of propranolol of 2.5 hr with mean plasma levels of propranolol peaking (Tmax) at 13.1 hr post-dose (-10:30 AM) for — 160 mg and at 10,6 hr post-dose (-8:30 AM) for Inderal® LA 160 mg. Neither group had measurable levels of propranolol before 1.5 hr post-dose, but there was a propranolol peak at approximately 6 hr post-dose in the Inderal LA 160 mg group while plasma propranolol increased at a consistent rate from 1.5 hr to 14 hr post-dose in the — 160 mg group.

- The maximal decreases in blood pressure occurred 8 hr to 9 hr post-dose (5:30 AM to 6:00 AM) in both groups, There were no incidents of postural hypotension during the study. Mean heart rate changes were not clinically meaningful. No deaths, serious adverse events, or premature withdrawals from treatment occurred during this study. No clinically significant changes were noted in hematology, clinical chemistry, or urinalysis parameters or for physical examinations or ECGs. The changes noted in vital signs were normal for healthy males in this age range and expected after the administration of a beta-adrenergic receptor-blocking antihypertensive agent. Overall, both formulations of propranolol were well

tolerated during the study.

REVIEWER COMMENTS:

1. *With respect to the bioassay for propranolol, the provided assay validation information and Quality Control data are appropriate and acceptable.*
2. *It should be noted that this was the first study (pilot) conducted with the to-be-marketed formulation to evaluate the preliminary pharmacokinetics and safety of [redacted] 160 mg relative to Inderal® LA 160 mg in healthy subjects. Based on the plasma concentration versus time curves for propranolol obtained in this study, blood collection times for future trials were selected.*

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10 pages redacted from this section of the approval package consisted of draft labeling

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Angelica Dorantes
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Patrick Marroum
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NDA 21-438
Reliant Pharmaceuticals' — (propranolol hydrochloride) Extended Release Capsules

PHARMACOLOGIST'S REVIEW OF LABELING

C.A. Resnick, Ph.D.
Supervisory Pharmacologist
Division of CardioRenal Drug Products (HFD-110)

This is a 505(b)(2) application for a new extended release formulation of propranolol HCl that is claimed to provide a different release profile from the previously approved product (Inderal® LA, Wyeth-Ayerst). The new formulation is said to have been designed to release propranolol in an extended release manner after a controlled 4-hour lag time for absorption into the gastrointestinal tract, and to provide peak concentrations 14 hours after dosing. Indications and treatment regimens (except for time of daily dosing) are the same as for Inderal LA. The Agency's finding of safety and efficacy for Inderal LA may be considered to extend to Reliant's new product. In view of the above, this 505(b)(2) application does not require evidence of safety from new in vitro or in vivo studies (none have been conducted) nor a formal pharm/tox review.

Regarding those sections of labeling that deal with nonclinical evaluations of the potential toxicity of propranolol HCl, the proposed labeling for Reliant's product mimics that of Inderal LA.

The following revisions are recommended for the labeling of both the Reliant and Wyeth-Ayerst products:

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/s/

Charles Resnick
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PHARMACOLOGIST