BPH.

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DEC 15 1999

NDA: 21-114

PRODUCT: Betaxon (levobetaxolol HCl) Ophthalmic Suspension, 0.5%

SUBMISSION DATES: 8/25/1999 12/07/99, 12/08/99

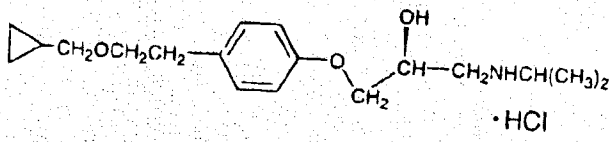
SPONSOR: Alcon
6201 S. Freeway, Fort Worth, TX 76134

TYPE OF SUBMISSION: Original, 1P

REVIEWER: Sue-Chih Lee, Ph.D.

BACKGROUND

Betaxolol is a β_1-selective adrenergic receptor blocking agent with calcium channel blocking activity. There are two approved ophthalmic drug products containing racemic betaxolol (i.e., Betoptic S Ophthalmic Suspension 0.25% and Betoptic Ophthalmic Solution 0.5%) which are indicated for lowering intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension. The mechanism of ocular hypotensive action is thought to be a reduction of aqueous humor production. The sponsor claims that levobetaxolol (S-isomer) is the more biologically active enantiomer of betaxolol and is primarily responsible for reducing intraocular pressure. The proposed product (Betaxon) containing the S-isomer is intended for the same indication as the racemate. The dosage is one drop in the affected eye(s) twice daily.



To support this NDA, the sponsor conducted a pharmacokinetic study in healthy subjects to determine the systemic absorption for three products (Betaxon Ophthalmic Suspension 0.5%, Betoptic Ophthalmic Solution 0.5% and Timolol Ophthalmic Solution 0.5%). Various literature articles that provide information on pharmacokinetic characteristics of betaxolol were also submitted.

LABELING COMMENTS

1. The information on timolol Cmax after administration of TIMOPTIC® (timolol) Ophthalmic Solution as included in the label can be misleading and, therefore, should be removed. The sponsor's label also lacks clarity in relation to dosing. We recommend the label to read as follows:

BETAXON Ophthalmic Suspension 0.5% (levobetaxolol), BETOPTIC® Ophthalmic Solution 0.5% (racemic betaxolol) and TIMOPTIC® Ophthalmic Solution 0.5% (timolol) were dosed at one drop each eye twice daily for 7 days to steady-state in a double-masked crossover study in 20 normal volunteers. Mean peak levobetaxolol plasma concentration (Cmax) was reached about three hours after dosing. The mean half-life of levobetaxolol from Betaxon was 19.7 ± 4.7 hours. At steady-state, levobetaxolol Cmax (0.547 ± 0.143 ng/mL) and $AUC_{0\text{-}12\ hr}$ (5.40 ± 1.40

ng*hr/mL) following administration of BETAXON Ophthalmic Suspension 0.5% were significantly ($p<0.05$) less than those observed for racemic betaxolol (Cmax 0.870 ± 0.425 ng/mL and $AUC_{0\text{-}12\ hr}$ 8.68 ± 4.46 ng*hr/mL) following administration of BETOPTIC® Ophthalmic Solution.

2. First sentence under "WARNING:"
Topically applied beta-adrenergic blocking agents may be absorbed systemically. We recommend [redacted] be changed to [redacted]

RECOMMENDATION

From the biopharmaceutics standpoint, the application is acceptable provided that the label is revised as indicated above. The labeling comments should be communicated to the sponsor.

APPEARS THIS WAY
ON ORIGINAL

/S/ 12/14/99

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Dennis Bashaw, Pharm.D. /S/ 12/15/99

CC:
NDA 21-114
HFD-550 (Div.File)
HFD-550 (CSO/Gorski)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

APPEARS THIS WAY
ON ORIGINAL

Table of Contents:

I. FORMULATION

The components and composition of the proposed product is given in the table below:

Ingredient	
Levobetaxolol Hydrochloride	
Benzalkonium Chloride	
Poly(styrene-divinylbenzene) Sulfonic Acid	
Carbomer 974P	
Mannitol	
Boric Acid	
Editate Disodium	
N-Lauroylsarcosine	
Tromethamine and/or HCl	
Purified Water	

II. ANALYTICAL METHOD

III. SUMMARY OF BIO/PK/PD CHARACTERISTICS

SYSTEMIC ABSORPTION OF LEVOBETAXOLOL, RACEMIC BETAXOLOL AND TIMOLOL

Protocol C-97-81: A Double-Masked, Three-Period Crossover, Multi-Dose Pharmacokinetic Study of Levobetaxolol 0.5% Ophthalmic Suspension Versus Betaxolol 0.5% Ophthalmic Solution and Timolol 0.5% Ophthalmic Solution Following Topical Ocular Administration on Normal Volunteers

Objectives: This study was conducted at [redacted] characterize the plasma pharmacokinetics of levobetaxolol, racemic betaxolol [redacted] and timolol following topical ocular administration to normal volunteers.

Study Design: The study was a randomized three-way crossover design involving 24 normal adult subjects, of which 20 subjects completed all treatments. The dosing regimen involved BID administration to both eyes for 1 week during each treatment arm with one of the following test articles: Levobetaxolol Ophthalmic Suspension, 0.5%, RS-betaxolol Ophthalmic Solution, 0.5% or Timolol Ophthalmic Solution, 0.5%. There was a 7-day washout period between treatments.

Sample collection: Plasma samples were collected immediately prior to dosing and 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 12 hours after the morning dose on Days 1 and 7.

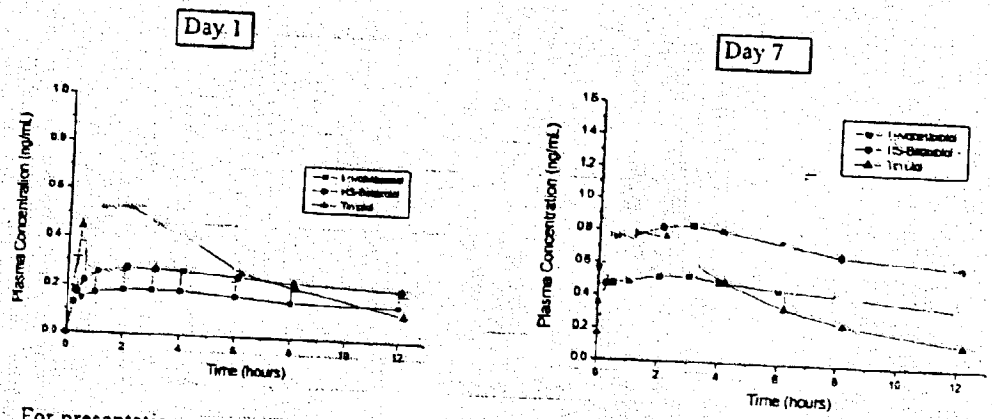
Assay: Plasma concentrations of levobetaxolol, RS-betaxolol and timolol were determined at [redacted] using [redacted] methods with [redacted] for levobetaxolol, betaxolol and timolol. The assay method for betaxolol was not [redacted] selective.

Data analysis: Pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-}12\ Hr}$ and $t_{1/2}$) were calculated using noncompartmental methods. The elimination half-life was calculated from the slope of the log concentration versus time profile using unweighted linear regression.

Results

Systemic exposure to parent drug from all three study medications was demonstrated following both single and multiple dosing. Mean plasma drug concentrations for Days 1 and 7 are shown in Figure 1.

Figure 1. Mean Plasma Concentrations of Levobetaxolol, RS-Betaxolol and Timolol



NOTE: For presentation purposes only, the timepoints of two of the curves were shifted slightly to make the standard deviation bars more visible.

Following topical ocular dosing of Levobetaxolol Suspenaion, mean (±SD) Cmax and AUC_{0-12} were 0.209±0.086 ng/mL and 1.93±0.81 ng.hr/mL, respectively, on Day 1 and increased to 0.547±0.143 ng/mL and 5.40±1.40 ng.hr/mL, respectively, on Day 7. Plasma pharmacokinetic parameters for all three formulations are summarized in Table 1.

Table 1: Mean (± %CV) Plasma Pharmacokinetic Parameters from Study C-97-81

Day 1

Test Article	C_{max} (ng/mL)	T_{max} (hours)	AUC_{0-12} (ng*hr/mL)	$T_{½}$ (hours)
Levobetaxolol	0.209 (41.1%)	3.3 (76%)	1.93 (42.0%)	19.5 (51.8%)
Betaxolol	0.299 (59.9%)	2.8 (61%)	2.88 (63.9%)	23.4 (47.0%)
Timolol	0.606 (57.7%)	1.1 (73%)	3.65 (64.4%)	4.96 (31.8%)

Day 7

Test Article	C_{max} (ng/mL)	T_{max} (hours)	AUC_{0-12} (ng*hr/mL)	$T_{½}$ (hours)
Levobetaxolol	0.547 (26.1%)	2.7 (66.7%)	5.40 (25.9%)	19.7 (23.8%)
Betaxolol	0.870 (48.8%)	3.0 (36.7%)	8.68 (51.4%*)	20.4 (37.2%)
Timolol	0.859 (78.7%*)	0.84 (65.5%)	4.89 (79.3%)	4.42 (23.5%*)

*Day 7 mean significantly different from corresponding parameter for levobetaxolol ($p < 0.05$).

Levobetaxolol Suspension vs. RS-betaxolol Solution:

Mean plasma betaxolol concentration following administration of Levobetaxolol Suspension was approximately [redacted] than that after administration of RS-betaxolol Solution. Statistical evaluation of the Day 7 pharmacokinetic results showed significant differences ($p < 0.05$) between levobetaxolol and RS-betaxolol for C_{max} and $AUC_{0-12\ hr}$. No significant differences in

T_{max} (~3 hrs) or $T_{½}$ (~20 hrs) were evident. The significantly lower bioavailability for levobetaxolol (lower C_{max} and $AUC_{0\text{-}12\ hr}$) relative to RS-betaxolol may be due to formulation differences between the two test articles (resin suspension for levobetaxolol versus solution for RS-betaxolol). (Note: The sponsor also compared levobetaxolol and timolol Day 7 data which showed significant differences in all parameters except $AUC_{0\text{-}12\ hr}$.)

Half-life:

Mean half-life of betaxolol observed in this topical ocular study (see Table 1) ranged from [redacted] Therefore, the Day 7 data represents steady state conditions. (These half-life values are within the range reported in the literature. For oral timolol, an elimination half-life of about 4 hours has been reported, similar to the mean half-life of about [redacted] observed in this study.)

Accumulation:

For levobetaxolol and RS-betaxolol, plasma drug concentrations following the initial dose were below 1 ng/mL in all cases. All three drugs showed accumulation over the 1-week dosing regimen, with increases in C_{max} of 2.6-, 2.9- and 1.4-fold for levobetaxolol, RS-betaxolol and timolol, respectively. The corresponding increases in mean $AUC_{0\text{-}12\ hr}$ were 2.8-, 3.0- and 1.3-fold, respectively. The degree of accumulation reflected in both C_{max} and $AUC_{0\text{-}12\ hr}$ is consistent with that expected at steady-state, based upon the observed mean half-lives. (Based on half-lives of 20 hours for levobetaxolol and RS-betaxolol and 5 hours for timolol, the predicted degree of accumulation to steady-state with BID administration is 2.9-fold for levobetaxolol and RS-betaxolol and 1.2-fold for timolol.)

Comments:

1. There is [redacted] betaxolol. Animal studies in rats (oral and iv dosing) and rabbits (topical ocular dosing) indicated no evidence of in vivo inversion of the S-isomer. [redacted] Further, the systemic exposure to betaxolol was lower from Betaxon than from betaxolol 0.5% Ophthalmic Solution.
2. For samples assaying below the quantitation limit, other than Day 1 pre-dose samples, a numerical value equal to the [redacted] was assigned for purposes of pharmacokinetic calculations. This will inflate AUC values slightly.

REVIEW OF LITERATURE ARTICLES

Drug Concentrations in Plasma and Aqueous Humor

A clinical study[1] determined drug concentrations (radioreceptor assay) in plasma and aqueous humor following single topical administration of 40 µL of either 0.5% betaxolol (n=15) or 0.25% timolol (n=15) to each eye in patients immediately prior to cataract surgery. Mean C_{max} was 1.1 ± 0.8 ng/mL for betaxolol (with mean Tmax of 89±79 min) and 1.36 ± 0.55 ng/mL for timolol. Approximately one hour after drug application, mean aqueous humor concentration was 4.1±1.4 µg/mL for betaxolol and 1.65±0.78 µg/mL for timolol. Cmax values for RS-betaxolol and timolol reported in this study were higher than those found in the Alcon study (1.1 vs.

0.30 ng/mL for betaxolol). However, the Alcon study was conducted in intact eyes, not eyes undergoing surgery. Note that the proposed formulation was not included in this study.

[1]M. L. Vuori, T. Ali-Melkilla, T. Kaila, E. Iisalo and K. M. Saari, "Plasma and Aqueous Humor Concentrations and Systemic Effects of Topical Betaxolol and Timolol in Man", Acta Ophthalmologica, 1993, 71, 201-206.

Oral and i.v. Studies of Racemate

The pharmacokinetics of RS-betaxolol following oral or i.v. administration to humans have been reported in the literature.

Ludden et al.,[2] evaluated the pharmacokinetics of RS-betaxolol in 12 normal subjects following a single 10 mg i.v. dose and 10, 20 and 40 mg oral doses. Dose proportional increases in C_{max} and $AUC_{0-\infty}$ were observed over the oral dose range. (Mean C_{max}: 21.6 ± 3.7 ng/mL for a 10 mg dose; 90.0 ± 16.0 ng/mL for the 40 mg dose. Mean $AUC_{0-\infty}$: 540 ± 128 to 2096 ± 492 ng*hr/mL.) The elimination half-life ranged from 13 to 20 hrs.

Bianchetti et al.,[3] evaluated the pharmacokinetics of RS-betaxolol following QD oral doses from 10 to 60 mg for up to 1 week. Dose-proportional pharmacokinetics was demonstrated over the dose range. Mean whole blood clearance ranged from 0.28 to 0.33 L/hour/kg and the elimination half-life ranged from about 16 to 22 hours. Steady-state was achieved in less than one week.

Balnave, et al.,[4] studied the pharmacokinetics and reduction in exercise-induced tachycardia of betaxolol and other beta-blockers in 5 normal volunteers. This study involved single oral doses over a 5- to 40-mg range. Dose-proportional increases in maximum blood concentrations were observed over the dose range, with maximum levels achieved between 3 and 8 hours post-dose. The mean elimination half-life was 24.5 ± 6.8 hours.

Maximum systemic exposure to racemic betaxolol in these published i.v. and oral studies was substantially higher (up to nearly 100-fold) than that found for levobetaxolol or racemate administered topically in the eye.

[2]T. M. Ludden, D. A. Boyle, D. Gieseker, G. T. Kennedy, M. H. Crawford, L. K. Ludden and W. A. Clementi. "Absolute Bioavailability and Dose Proportionality of Betaxolol in Normal Healthy Subjects", J. Pharm. Sci., 1988, 77 (9), 779-783.

[3]G. Bianchetti, C. Blatrix, R. Gomeni, J. R. Kilborn, J. Larribaud, P. W. Lucker, J. J. Thebault, S. Trocherie and P. L. Morselli, "Pharmacokinetics of the New β-Adrenoreceptor Blocking Agent Betaxolol (SL 75212) in Man After Repeated Oral Administration", Arzneim. Forsch. 1980, 30, 1912-1916.

[4]K. Balnave, J. D. Neill, C. J. Russel, D. W. G. Harron, W. J. Leahey, R. Wilson and R. G. Shanks, "Observations on the Efficacy and Pharmacokinetics of Betaxolol (SL 75212), a Cardioselective β-Adrenoreceptor Blocking Agent", Br. J. Clin. Pharmacol., 1981, 11, 171-180.

Pharmacokinetics of Individual Enantiomers Following Administration of Racemate

The human pharmacokinetics of the R and S enantiomers of betaxolol following oral dosing of the racemate have been investigated by analysis of blood samples using chiral liquid chromatographic methods.[5-6] In one study,[5] twelve volunteers each received a single 10 mg racemic betaxolol dose in a 30 minute IV infusion and blood samples were collected over a 48-hour period. On a separate visit, the same subjects received a single 40 mg oral dose of racemic betaxolol, again with blood sampling over 0-48 hours post-dose. Pharmacokinetic profiles of the R and S enantiomers were virtually identical and no significant stereoselective differences were found in clearance, volume of distribution and elimination rate for either route of administration. In another study,[6] three subjects received a single oral dose of 20 mg RS-betaxolol along with the diuretic chlorthalidone. Peak whole blood concentrations for each isomer were achieved within 3 hours and were approximately 20 ng/mL. The blood concentration versus time profiles for the two enantiomers in a given subject over 0-72 hours were virtually superimposable, indicating no stereoselectivity in human systemic pharmacokinetics for RS-betaxolol.

[5]G. Stagni, P. J. Davis and T. M. Ludden, "Human Pharmacokinetics of Betaxolol Enantiomers", J. Pharm. Sci., 1991, 80, 321-324.

[6]A. Darmon and J. P. Thenot, "Determination of Betaxolol Enantiomers by High-Performance Liquid Chromatography: Application to Pharmacokinetic Studies", J. Chromatogr. Biomed. Appl., 1986, 374, 321-328.

Protein Binding, Metabolism and Elimination

Levobetaxolol exhibits relatively low binding to human plasma proteins. An *in vitro* protein binding study in human plasma using ultrafiltration method showed ^{3}H-levobetaxolol to be approximately 50% bound to plasma proteins over the concentration range 1-1000 ng/mL.[7] In the same experiment, the plasma binding of ^{3}H racemic betaxolol was shown to be 47% bound at a 10 ng/mL concentration. These results suggest a similar degree of protein binding between the racemate and the S-isomer.

The metabolism and elimination of racemic betaxolol in humans has been investigated following a single 20 mg oral dose of ^{14}C-betaxolol.[8] The majority of the urinary recovery of the radioactive dose (76-83%) occurred within 7 days after dosing. Only trace amounts (1-3% of the dose) were recovered in feces. The predominant metabolic route of betaxolol in man involves formation of the isopropyl-amino moiety with oxidation of the carbon alpha to the hydroxyl group to a carboxylic acid. This metabolite accounts for about 35% of the dose in the urine. The other principal metabolite is formed by loss of the cyclopropyl-methyl group, accompanied by oxidation of the resulting alcohol to a carboxylic acid. This route reflects about 24% of the dose in urine. Most of the remaining drug related material in urine is parent drug (about 16% of the dose). Betaxolol and its metabolites are not found in conjugated forms in human urine. Since these metabolic routes do not involve the chiral center of the molecule, a similar metabolic profile for levobetaxolol and the racemate in humans is expected..

[7]M. E. Sanders, "*In Vitro* Protein Binding of ^{3}H-Levobetaxolol and ^{3}H-Betaxolol in Human, Rat, Rabbit and Monkey Plasma", Alcon Technical Report 026:38570:0499.

[5]B. Ferrandes, A. Durand, J. Anre-Fraisse, J. Thenot and P. Hermannn, "Pharmacokinetics and Metabolism of Betaxolol in Various Animal Species and Man", L.E.R.S. Monograph Series, volume I, P. L. Morselli et al., (eds), Raven Press, NY, 1983, 51-64.

CONCLUSIONS

1. Following topical ocular administration of Levobetaxolol Suspenaion, mean (±SD) steady state Cmax and AUC_{0-12} were 0.547±0.143 ng/mL and 5.40±1.40 ng.hr/mL, respectively, which were approximately [redacted] than those from 0.5% RS-betaxolol Ophthalmic Solution (BETOPTIC). The lower systemic exposure from Betaxon relative to Betoptic Opthalmic Solution may be primarily due to formulation differences.

2. Both levobetaxolol and racemate betaxolol exhibited comparable elimination half-life of approximately 20 hours resulting in an accumulation ratio of [redacted] at steady-state following BID topical administration. Literature data involving chiral bioanalysis following oral or i.v. administration of racemic betaxolol to humans demonstrated comparable pharmacokinetics of the two enantiomers.

3. Levobetaxolol exhibits moderate plasma protein binding (50%) in humans. Clinical trials using oral racemic betaxolol have shown the drug to be biotransformed via oxidative pathways to two inactive metabolites, which are excreted in the urine. The known metabolic pathways of betaxolol in man do not involve modification of the chiral center of the molecule.

4. Following topical ocular administration, plasma concentrations of levobetaxolol and racemic betaxolol are much [redacted] than whole blood concentrations from clinical therapeutic oral doses of the racemate.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 1

Individual Data (Protocol C-97-81)

Table 1:

Plasma Pharmacokinetic Parameters for 0.5% Ophthalmic Levobetaxolol, Day 1

Subject No.	Period	Cmax (ng/mL)	Tmax (hr)	$AUC_{0\text{-}12\ hour}$ (ng x hr /mL)	$T_{1/2}$ (hr)
2001	3				
2002	1				
2004	2				
2005	2				
2006	1				
2007	2				
2008	3				
2009	2				
2010	1				
2011	1				
2012	3				
2014	1				
2015	2				
2016	1				
2017	2				
2018	3				
2019	2				
2020	1				
2022	2				
2023	3				
2024	1				
Mean		0.209	3.3	1.93	19.5
S.D.		0.086	2.5	0.81	10.1
C.V. (%)		41.1	75.8	42.0	51.8

NC = Not calculated – terminal phase of plasma concentration versus time profile did not exhibit negative slope making estimation of terminal half-life unfeasible.

Table 2:

Plasma Pharmacokinetic Parameters for 0.5% Ophthalmic RS-Betaxolol, Day 1

Subject No.	Period	Cmax (ng/mL)	Tmax (hr)	$AUC_{0\text{-}12\ hour}$ (ng x hr /mL)	$T_{1/2}$ (hr)
2001	1				
2002	3				
2004	1				
2005	3				
2006	2				
2007	1				
2008	1				
2009	3				
2010	3				
2011	2				
2012	2				
2013	1				
2014	3				
2015	1				
2016	2				
2017	3				
2018	2				
2019	3				
2020	3				
2022	1				
2023	1				
2024	2				
Mean		0.299	2.8	2.88	23.4
S.D.		0.179	1.7	1.84	11.0
C.V. (%)		59.9	60.7	63.9	47.0

Table 3:

Plasma Pharmacokinetic Parameters for 0.5% Ophthalmic Timolol, Day 1

Subject No.	Period	Cmax (ng/mL)	Tmax (hr)	$AUC_{0\text{-}12\ hour}$ (ng x hr /mL)	$T_{1/2}$ (hr)
2001	2				
2002	2				
2003	1				
2004	3				
2005	1				
2006	3				
2007	3				
2008	2				
2009	1				
2010	2				
2011	3				
2012	1				
2014	2				
2015	3				
2016	3				
2017	1				
2018	1				
2019	1				
2020	2				
2022	3				
2023	2				
2024	3				
Mean		0.606	1.1	3.65	4.96
S.D.		0.350	0.8	2.35	1.58
C.V. (%)		57.8	72.7	64.4	31.8

Table 4

Plasma Pharmacokinetic Parameters for 0.5% Ophthalmic Levobetaxolol BID for 1 Week, Day 7

Subject No.	Period	Cmax	Tmax	$AUC_{0\text{-}12\ hour}$	$T_{1/2}$
2001	3				
2002	1				
2004	2				
2005	2				
2006	1				
2007	2				
2008	3				
2009	2				
2010	1				
2011	1				
2014	1				
2015	2				
2016	1				
2017	2				
2018	3				
2019	2				
2020	1				
2022	2				
2023	3				
2024	1				
Mean		0.547	2.7	5.40	19.7
S.D.		0.143	1.8	1.40	4.7
C.V. (%)		26.1	66.7	25.9	23.8

Table 5:

Plasma Pharmacokinetic Parameters for 0.5% Ophthalmic RS-Betaxolol BID for 1 Week, Day 7

Subject No.	Period	Cmax (ng/mL)	Tmax (hr)	$AUC_{0\text{-}12\ hour}$ (ng x hr /mL)	$T_{1/2}$ (hr)
2001	1				
2002	3				
2004	1				
2005	3				
2006	2				
2007	1				
2008	1				
2009	3				
2010	3				
2011	2				
2012	2				
2013	1				
2014	3				
2015	1				
2016	2				
2017	3				
2018	2				
2019	3				
2020	3				
2022	1				
2023	1				
2024	2				
Mean		0.870	3.0	8.68	20.4
S.D.		0.425	1.1	4.46	7.6
C.V. (%)		48.8	36.7	51.4	37.2

Table 6:

Plasma Pharmacokinetic Parameters for 0.5% Ophthalmic Timolol BID for 1 Week, Day 7

Subject No.	Period	Cmax (ng/mL)	Tmax (hr)	$AUC_{0\text{-}12\ hour}$ (ng x hr /mL)	$T_{1/2}$ (hr)
2001	2				
2002	2				
2003	1				
2004	3				
2005	1				
2006	3				
2007	3				
2008	2				
2009	1				
2010	2				
2011	3				
2012	1				
2014	2				
2015	3				
2016	3				
2017	1				
2018	1				
2019	1				
2020	2				
2022	3				
2023	2				
2024	3				
Mean		0.859	0.8	4.89	4.42
S.D.		0.676	0.6	3.88	1.04
C.V. (%)		78.7	75.0	79.3	23.5