CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-818

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	50-818
Submission Date(s):	14JUN2007
Brand Name	TobraDex®-ST
Generic Name	Tobramycin 0.3% and Dexamethasone 0.05%
Primary Reviewer	Kimberly L. Bergman, Pharm.D.
Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Alcon Research, Ltd.
Relevant IND(s)	IND 72,063
Submission Type; Code	505(b)(2) application
Formulation; Strength(s)	Tobramycin 0.3% and Dexamethasone 0.05% ophthalmic suspension
Indication	Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial infection exists

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1. EXECUTIVE SUMMARY

TobraDex®-ST, tobramycin 0.3%/dexamethasone 0.05% ophthalmic suspension, is an antibiotic/ anti-inflammatory combination product containing the aminoglycoside, tobramycin, and the corticosteroid, dexamethasone formulated for ophthalmic use. The proposed indication for TobraDex®-ST is treatment of steroid-responsive inflammatory ocular conditions for which a steroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. The proposed dosage and route of administration for TobraDex®-ST is as follows: instill one drop into the conjunctival sac every 4 to 6 hours. During the initial 24 to 48 hours, dosage may be increased to one drop every 2 hours.

The active components of TobraDex®-ST are available in the currently marketed ophthalmic product TobraDex®. TobraDex® was first approved in the US in 1988 (NDA 50-592) and is also marketed in Canada, most EU countries, and over 102 other countries worldwide. The clinical efficacy and safety of TOBRADEX have previously been established. TobraDex®-ST contains the same concentration of tobramycin (0.3%) as TobraDex® and half the dexamethasone concentration of TobraDex® (0.05% vs. 0.1%). TobraDex®-ST includes a retention-enhancing agent, xanthan gum, allowing use of a lower dexamethasone concentration to achieve equivalent dexamethasone aqueous humor exposure to that of TobraDex®.

To support product approval, the Applicant's objective was to demonstrate bioequivalence of dexamethasone in aqueous humor following administration of TobraDex®-ST versus TobraDex®. Supporting studies were to include an *in vitro* kill rate study to demonstrate comparable bactericidal kinetics between TobraDex®-ST and TobraDex®. Three clinical trials were conducted in the U.S. to support the bioequivalence of TobraDex®-ST to TobraDex®: a pilot aqueous humor bioavailability study (C-05-43) and two aqueous humor bioequivalence studies (C-05-23 and C-06-37) involving 2100 cataract surgery patients. This Clinical Pharmacology review focused specifically on the pivotal bioequivalence Study C-06-37. In addition, the Applicant submitted a Phase 1 systemic pharmacokinetic study with TobraDex® (C-99-33), which was also addressed in this Clinical Pharmacology review. Based on Applicant and FDA analysis of dexamethasone data obtained from Study C-06-37, the proposed drug product TobraDex®-ST, tobramycin 0.3%/dexamethasone 0.05% ophthalmic suspension, met the criteria for equivalence for the primary pharmacokinetic parameter AUC_{0-5} compared to the reference product TobraDex®. The data submitted by the Applicant supports approval of the product from a Clinical Pharmacology perspective.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant supports approval of the drug product based on equivalence for dexamethasone in aqueous humor following administration of TobraDex®-ST and TobraDex®.

1.2. Phase IV Commitments

Not applicable.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

TobraDex®-ST, tobramycin 0.3%/dexamethasone 0.05% ophthalmic suspension, is an antibiotic/ anti-inflammatory combination product containing the aminoglycoside, tobramycin, and the

corticosteroid, dexamethasone formulated for ophthalmic use. To support product approval, a pivotal bioequivalence study for dexamethasone in aqueous humor following administration of TobraDex®-ST versus the commercially available reference product (TobraDex®) was conducted. Supporting studies included assessment of *in vitro* kill rate to demonstrate comparable bactericidal kinetics between TobraDex®-ST and TobraDex®.

Based on Applicant and FDA analysis of dexamethasone aqueous humor concentrations obtained up to 5 hours post dose (AUC_{0-5}) in Study C-06-37, the proposed drug product TobraDex®-ST (tobramycin 0.3%/ dexamethasone 0.05%) ophthalmic suspension met the criteria for equivalence for the primary pharmacokinetic parameter AUC_{0-5} compared to the reference product TobraDex®. The 90% confidence interval (0.983, 1.16) around the ratio (1.07) of the aqueous humor dexamethasone AUC_{0-5} values for TobraDex®-ST and TobraDex® were within 0.80 to 1.25, demonstrating that the two formulations are equivalent. Agency analyses of partial areas support equivalence of the two products for the exposure parameters AUC_{0-2}, AUC_{0-3}, and the primary parameter AUC_{0-5}. The upper bound of the calculated 90% confidence interval for the comparison of AUC_{0-1} fell outside the pre-specified 80 to 125% interval; the 90% confidence limits were 90.6% to 126.8% for AUC_{0-1}. Because the upper bound of the 90% confidence interval for AUC_{0-1} ***exceeded*** 125% (i.e. dexamethasone concentrations were higher with the test product), it is unlikely this finding would have a negative impact on efficacy compared to the reference product. Safety information from patients administered TobraDex®-ST prior to cataract surgery, data following long-term, multiple dose administration of TobraDex®, and the safety profile following systemic administration of much higher doses of dexamethasone support the conclusion that the upper bound for the AUC_{0-1} comparison of 126.8% is not expected to be clinically relevant from a safety standpoint. In summary, the data submitted by the Applicant supports approval of the product from a Clinical Pharmacology perspective.

Kimberly L. Bergman, Pharm.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology 4

Concurrence:

Charles R. Bonapace, Pharm.D.
Team Leader

cc:
Division File: NDA 50-818
HFD-520 (CSO/Rodriguez)
HFD-520 (MO/Lim)
HFD-520 (Chambers, Boyd)
HFD-880 (Lazor, Reynolds, Bonapace)

2. QUESTION BASED REVIEW

Since this submission is a 505(b)(2) NDA for a locally administered product relying upon conclusions drawn by the Agency for a previously approved ophthalmic product, only relevant questions from the OCP question-based review (QBR) format are addressed below.

2.1. General Attributes of the Drug

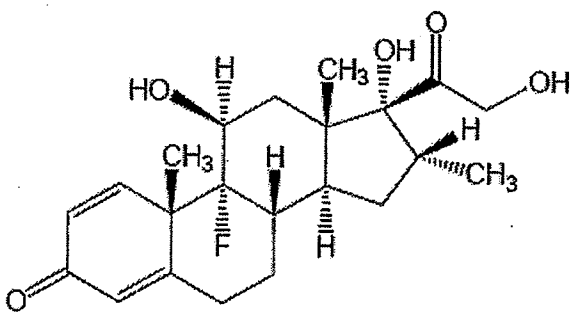
2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

TobraDex®-ST, tobramycin 0.3%/dexamethasone 0.05% ophthalmic suspension, is a sterile, isotonic, multi-dose ophthalmic suspension formulation preserved with benzalkonium chloride. The product was developed using the same active ingredients and preservative as TobraDex® Suspension (tobramycin 0.3%/dexamethasone 0.1% ophthalmic suspension). TobraDex®-ST has a lower concentration of dexamethasone and an added retention-enhancing vehicle, which is designed to allow the formulation to provide similar efficacy as the marketed TobraDex® for the same indication.

The chemical structure and physical-chemical properties of dexamethasone are as follows:

Structural Formula: $C_{22}H_{29}FO_5$

Chemical Structure:



Chemical Name: Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-,(11β, 16α)-

Or

9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione

Compendial Name: Dexamethasone (USP, Ph. Eur.)

USAN/INN: Dexamethasone

Company Laboratory Code: AL-817

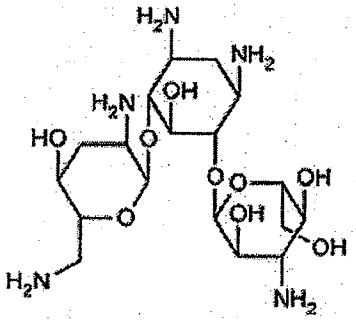
Chemical Abstract Service (CAS) Registry Number: 50-02-2

Molecular Weight: 392.47

The chemical structure and physical-chemical properties of tobramycin are as follows:

Structural Formula: $C_{18}H_{37}N_5O_9$

Chemical Structure:



Chemical Name: D-Streptamine, *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(1→4)]-2-deoxy-

Or

O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6-diamino-2,3,6- trideoxy-α-D-*ribo*-hexopyranosyl-(1→6)-2-deoxy-L-streptamine

Compendial Name: Tobramycin (USP, Ph. Eur.)

USAN/INN: Tobramycin

Chemical Abstract Service (CAS) Registry Number: 32986-56-4

Molecular Weight: 467.52

The quantitative composition of the proposed TobraDex®-ST drug product is shown in Table 2.2-1.

Table 2.2-1 Composition of TobraDex®-ST Ophthalmic Suspension

Component	% W/V	Function
Tobramycin, USP	0.3	Active
Dexamethasone ——— USP	0.05	Active
Benzalkonium Chloride, NF	0.01	Preservative
Edetate Disodium Dihydrate (EDTA), USP		———
Xanthan Gum, NF		Viscosity agent
Propylene Glycol, USP		
Sodium Sulfate, USP		
Sodium Chloride, USP		
Tyloxapol, USP		
Sodium Hydroxide, NF and/or Hydrochloric Acid, NF		pH adjuster
Purified water, USP	q.s. to 100%	———

Source: Section 2.3.P.1

b(4)

The formulation for TobraDex®-ST is similar to the currently marketed TobraDex®, as presented in Table 2.2-2. The viscosity modifying agent in the currently marketed TobraDex® (i.e., hydroxyethyl cellulose) was replaced with xanthan gum, — The concentrations of ——— , sodium chloride and sodium sulfate (anhydrous), were ⌜ ⌟ in the marketed TobraDex® formulation. In addition, sodium chloride concentration can be ——— to achieve the desired viscosity of the finished product due to its effect on xanthan gum. Propylene glycol at a concentration of —— was added to proposed formula for further adjustment of the —— without increasing the ionic strength. Both formulations contain tyloxapol as a ——— for the suspended dexamethasone, and benzalkonium chloride 0.01% as a preservative agent with disodium edetate ⌜ ⌟ Sodium hydroxide and hydrochloric acid (instead of sulfuric acid) are used to adjust the pH, while purified water is used as the ——

b(4)

Table 2.2-2 Comparison of TobraDex®-ST and TobraDex® Compositions

Ingredient	Composition	
	TOBRADEX Suspension (w/v%)	Tob 0.3% / Dex 0.05% Suspension (FID 109442) (w/v%)
Tobramycin	0.3	Same
Dexamethasone	0.1	0.05
Benzalkonium Chloride	0.01	Same
Hydroxyethyl Cellulose		None
Tyloxapol		Same
Disodium Edetate		Same
Sodium Chloride		
Sodium Sulfate (Anhydrous)		
Xanthan Gum	None	
Propylene Glycol	None	
Sodium Hydroxide	Adjust pH	Same
Sulfuric Acid	Adjust pH	None
Hydrochloric Acid	None	Adjust pH 5.7
Purified Water	q.s. 100	Same

b(4)

Source: Section 2.3.P.2

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

TobraDex®-ST is a corticosteroid (dexamethasone) and aminoglycoside antibiotic (tobramycin) combination. Corticosteroids suppress the inflammatory response by inhibiting or disrupting the action of leukocytes and other mediators of inflammation including cytokines, chemokines, lipid and glucolipid agents, and macrophages. Corticosteroids further affect the inflammatory process by inhibiting prostaglandin and leukotriene production through the reduction of cyclooxygenase and lipoxygenase, respectively, as well as disrupting platelet-activating factor synthesis resulting from inhibition of phospholipase A2. Dexamethasone is a long-acting glucocorticoid that, on the basis of weight, has approximately 27 times the antiflammatory potency of hydrocortisone. Since corticosteroids may inhibit the body's defense mechanism against infection, the antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms. In vitro studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms: Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains; Streptococci, including some of the Group A beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae; Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii*, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata*, and *Acinetobacter calcoaceticus* and some *Neisseria* species.

TobraDex®-ST is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

2.1.3. What is the proposed dosage and route of administration?

The proposed dosage and route of administration for TobraDex®-ST is as follows: instill one drop into the conjunctival sac every 4 to 6 hours. During the initial 24 to 48 hours, dosage may be increased to one drop every 2 hours.

2.2. General Clinical Pharmacology and Biopharmaceutics

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?

To support product approval, the Applicant's objective was to demonstrate bioequivalence of dexamethasone in aqueous humor following administration of TobraDex®-ST versus the marketed product TobraDex®. The test product contains the same concentration of tobramycin (0.3%) and a two-fold lower dexamethasone concentration than that of TobraDex® (0.05% vs. 0.1%). The TobraDex®-ST formulation includes a retention-enhancing agent, xanthan gum, that allows the use of a lower dexamethasone concentration to achieve equivalent dexamethasone aqueous humor exposure to that of TobraDex®. Supporting studies included assessment of *in vitro* kill rate to demonstrate comparable bactericidal kinetics between TobraDex®-ST and TobraDex®.

Three clinical trials were conducted in the U.S. to support the bioequivalence of TobraDex®-ST to TobraDex®: a pilot aqueous humor bioavailability study (C-05-43) and two aqueous humor bioequivalence studies (C-05-23 and C-06-37) involving 2100 cataract surgery patients.
In the pilot bioavailability study C-05-43, formulations with dexamethasone concentrations of 0.025% and 0.05% were compared to TobraDex®. Based on the results of this study, a dexamethasone concentration of 0.033% was selected for study in a larger bioequivalence trial (C-05-23) in 987 cataract surgery patients. The results of study C-05-23 demonstrated lower dexamethasone aqueous humor exposure in patients who were dosed with the tobramycin 0.3%/ dexamethasone 0.033% combination relative to TobraDex®. Based on the information from Studies C-05-43 and C-05-23, the pivotal bioequivalence study was designed to compare the formulation with the highest concentration of dexamethasone (0.05%) to the marketed product TobraDex® in a large population of cataract patients (n = 983) with more intensive PK sampling time points compared to the pilot study. This Clinical Pharmacology review focused specifically on this pivotal bioequivalence study with the to-be-marketed concentration of dexamethasone (0.05%), Study C-06-37. The formulation used in the pivotal bioequivalence study is identical to that proposed for marketing.

C-06-37 was a multi-center, double-masked, parallel-group, single-dose study in male and female patients, 18 years of age and older, requiring cataract surgery. The primary objective of this study was to demonstrate the bioequivalence of TobraDex®-ST Suspension (tobramycin 0.3%/ dexamethasone 0.05%) and TobraDex® Suspension (tobramycin 0.3%/dexamethasone 0.1%). Nine hundred eighty seven (987) patients were randomized to receive one topical ocular dose of TobraDex®-ST or TobraDex®. At 0.5, 1, 2, 3, or 5 hours post-dose, an aqueous humor sample was collected during cataract surgery, and the concentration of dexamethasone in the sample was measured. The primary pharmacokinetic parameter was the area under the concentration-time curve up to the last measured concentration (AUC_{0-5}). Primary inference was based on the construction of a two-sided 90% confidence interval about the ratio of AUC_{0-5} values. The per protocol population was considered the primary analysis population. Data analyses were also performed on the intent-to-treat data set using the three different imputation methods. The

Applicant used both the Fieller's method and the bootstrap method to estimate the 90% confidence interval for the ratio of AUC_{0-5} of the test product versus the reference product for per protocol and intent-to-treat populations.

In addition, the Applicant submitted a Phase 1 systemic pharmacokinetic study with TobraDex® (C-99-33), to support statements in the proposed label. C-99-33 was a single-center, open-label study designed to evaluate the pharmacokinetics of dexamethasone and tobramycin in plasma following multiple bilateral administration with TobraDex® in healthy subjects. This study demonstrated minimal plasma exposure of dexamethasone following multiple bilateral dosing of TobraDex® for two consecutive days in healthy male and female subjects. For additional information, a complete review of Study C-99-33 is included in Appendix 4.1.

2.2.2. Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?

The active moiety dexamethasone was appropriately identified and measured in aqueous humor for purposes of equivalence comparison. Refer to Section 2.3 for further details regarding the analytical methodology and performance for assay of dexamethasone in aqueous humor for the pivotal bioequivalence study.

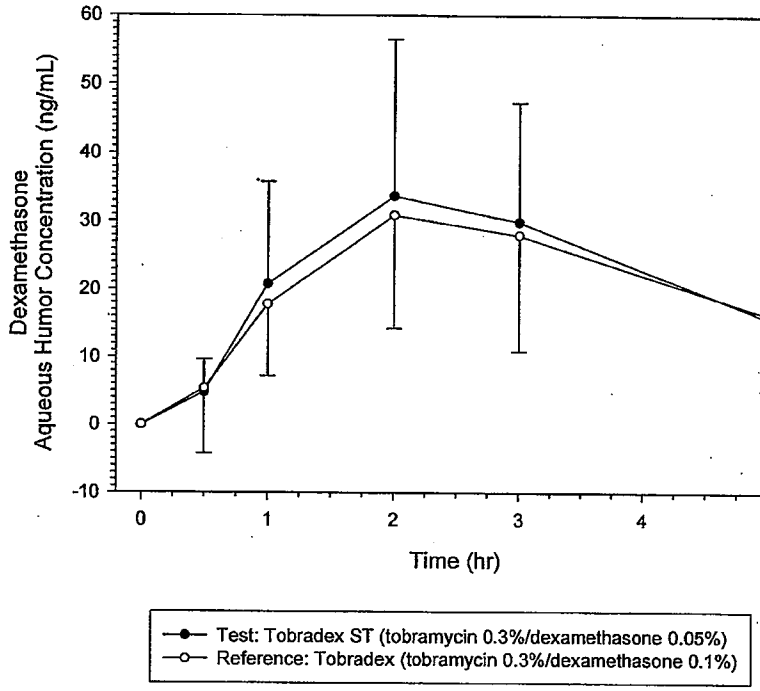
Dexamethasone was appropriately identified and measured in plasma for purposes of describing systemic exposure following ocular administration of TobraDex®. Based on review of assay performance results, the immunoassay used to measure tobramycin in plasma was inadequate for purposes of describing systemic exposure following ocular administration of TobraDex®. Thus, tobramycin plasma concentration data obtained in Study C-99-33 should not be used for regulatory purposes, including product labeling. For additional information on analytical methodology and performance for these assays, refer to the study review for C-99-33 in Appendix 4.1.

2.2.3. Is bioequivalence of the proposed product to the reference product demonstrated?

Based on the Applicant's analysis and FDA analysis of dexamethasone aqueous humor concentration data obtained from Study C-06-37, the comparison of the test product TobraDex®-ST versus the reference product TobraDex® met the equivalence limits of 80 to 125% for the primary pharmacokinetic parameter AUC_{0-5}.

Mean aqueous humor concentrations of dexamethasone following administration of the proposed drug product TobraDex®-ST (tobramycin 0.3%/dexamethasone 0.05%) to the reference product TobraDex® Suspension (tobramycin 0.3%/dexamethasone 0.1%) are displayed in Figure 2.2.3-1. Mean dexamethasone aqueous humor concentrations were similar between the two treatments. The maximum mean concentration (Cmax) was observed at 2 hours for both test and reference products.

Figure 2.2.3-1. Mean Dexamethasone Aqueous Humor Concentrations Versus Time from Cataract Patients Following a Single Unilateral Topical Ocular Dose of Tobramycin 0.3%/Dexamethasone 0.05% or TOBRADEX (Per Protocol Analysis)



Source: Clinical Study Report C-06-37, Table 11.4.1.1-1.

A summary of the results of the Applicant's bioequivalence assessment is presented in Table 2.2.3-1. The 90% confidence interval (0.983, 1.16) around the ratio (1.07) of the aqueous humor dexamethasone AUC_{0-5} values for TobraDex®-ST (tobramycin 0.3%/dexamethasone 0.05%) ophthalmic suspension and TobraDex® Suspension (tobramycin 0.3%/dexamethasone 0.1%) were within 0.80 to 1.25, demonstrating that the two formulations are equivalent. Both analysis populations (per protocol and ITT) and analysis methods (Fieller's and bootstrap) showed similar results. The ratio of Cmax values was determined as a secondary parameter of relative aqueous humor exposure between TobraDex®-ST and TobraDex®. The mean Cmax was observed at 2 hours for both formulations and is comparable as reflected by a ratio of 1.09 in the per protocol population; similar results were observed for the intent-to-treat data set.

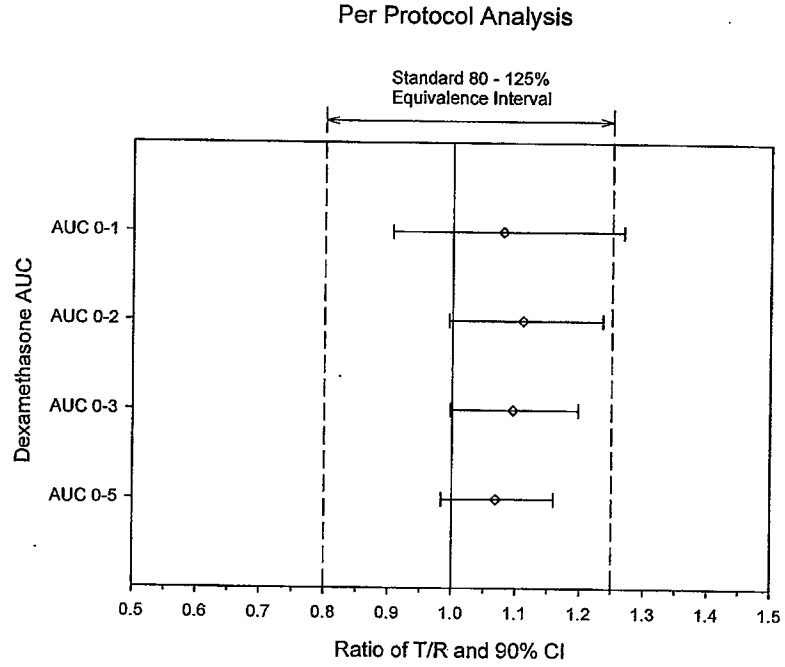
Table 2.2.3-1 Ratios and 90% Confidence Intervals for Dexamethasone AUC Values Following Administration of TobraDex®-ST (Tobramycin 0.3%/ Dexamethasone 0.05% [Test]) and TobraDex® (tobramycin 0.3%/dexamethasone 0.1% [Reference])

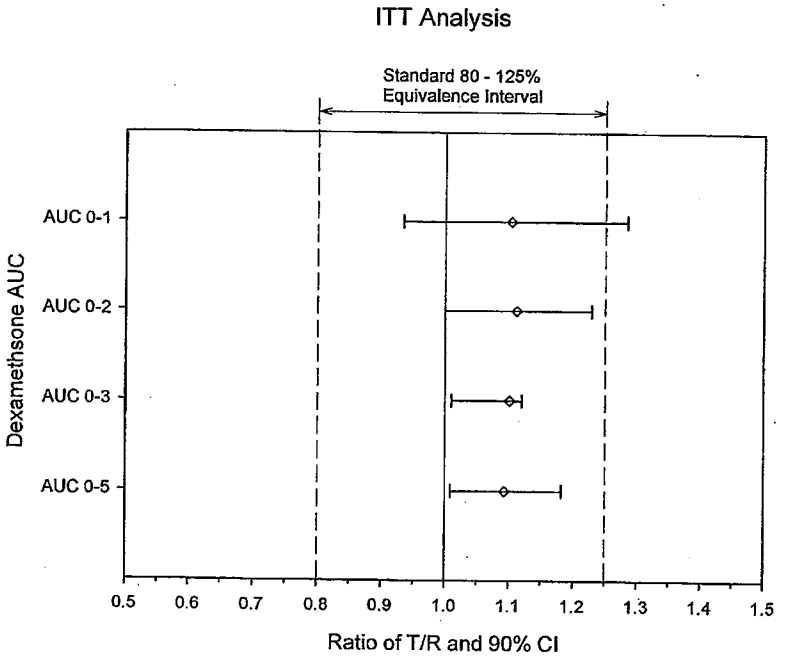
Analysis Method	*Dexamethasone AUC_{0-5}*			*90% CI*	
	Test	*Reference*	*Ratio*	*Lower Bound*	*Upper Bound*
Fieller's (per protocol)	112	105	1.07	0.983	1.16
Fieller's (ITT)	113	104	1.09	1.01	1.18
Bootstrap (per protocol)	112	105	1.07	0.996	1.19
Bootstrap (ITT)	113	104	1.09	1.01	1.20

Test, TobraDex®-ST (Tobramycin 0.3%/ Dexamethasone 0.05%)
Reference, TobraDex® (tobramycin 0.3%/dexamethasone 0.1%)
Source: Clinical Study Report C-06-37, Section 14.2.1.3.

A summary of the results of the Agency's bioequivalence assessment is presented in Figure 2.2.3-2. The Agency's analysis consisted of estimation of 90% confidence intervals via bootstrapping for the partial areas AUC_{0-1}, AUC_{0-2}, and AUC_{0-3}, in addition to the primary pharmacokinetic parameter for comparison AUC_{0-5}. The results support equivalence of the two products for the parameters AUC_{0-2}, AUC_{0-3}, and the primary parameter AUC_{0-5}. The upper bound of the calculated 90% confidence interval for the comparison of AUC_{0-1} fell outside the pre-specified 80 to 125% interval; the 90% confidence limits were 90.6% to 126.8% for AUC_{0-1}.

Figure 2.2.3-2. Ratios and 90% CI for the Comparison of Test [T; TobraDex®-ST (Tobramycin 0.3%/ Dexamethasone 0.05%)] to Reference [R; TobraDex® (Tobramycin 0.3%/Dexamethasone 0.1%)] in Study C-06-37





In conclusion, based on both the Applicant's analysis and the FDA analysis of dexamethasone aqueous humor concentration data obtained from Study C-06-37, the comparison of the test product TobraDex®-ST versus the reference product TobraDex® met the equivalence limits of 80 to 125% for the primary pharmacokinetic parameter AUC_{0-5} for both the per protocol and ITT populations. Results from additional analyses performed by the FDA support equivalence of the two products for the parameters AUC_{0-2}, AUC_{0-3}, and the primary parameter AUC_{0-5}. Although the upper bound for the AUC_{0-1} comparison was outside the limits, the actual ratios for all AUC comparisons were similar, suggesting this finding was due to the variability in calculated AUC_{0-1} values from bootstrapping. Because the upper bound of the 90% confidence interval for AUC_{0-1} ***exceeded*** 125% (i.e. dexamethasone concentrations were higher with the test product), it is unlikely this finding would have a negative impact on efficacy compared to the reference product. From a safety standpoint, no safety issues were identified in association with a single dose of TobraDex®-ST administered prior to cataract surgery based upon a review of adverse events and an assessment of ocular parameters from the bioequivalence study. TobraDex®-ST and TobraDex® exhibited similar safety profiles in Study C-06-37. The long-term safety profile following multiple dosing of TobraDex® has been well-established, as has the safety profile following systemic administration of much higher doses of dexamethasone. Thus, an upper bound for the AUC_{0-1} comparison of 126.8% is not expected to be clinically relevant from a safety standpoint, and the Applicant adequately established equivalence of the two products based on the primary comparison of AUC_{0-5}.

2.2.3.1. What are the safety or efficacy issues, if any, for a BE study that fails to meet the 90% CI using equivalence limits of 80 to 125%?

Although the upper bound of the calculated 90% confidence interval for the comparison of AUC_{0-1} fell outside the pre-specified 80 to 125% interval; there are no safety or efficacy concerns for this finding (see Section 2.2.3).

2.2.3.2. If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the proposed product?

The proposed formulation TobraDex®-ST met the criteria for equivalence for the primary pharmacokinetic parameter AUC_{0-5} compared to the reference product TobraDex®. This data submitted by the Applicant supports approval of the product from a Clinical Pharmacology perspective.

2.2.3.3. What other significant issues related to in vivo BE need to be addressed?

There are no other significant issues related to in vivo BE that need to be addressed.

2.3. Analytical Section

2.3.1. How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

The active moiety dexamethasone was identified and measured in aqueous humor by an HPLC tandem mass spectrometry (HPLC/MS/MS) method.

2.3.2. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total dexamethasone concentrations were measured in the aqueous humor of subjects receiving treatment in bioequivalence study C-06-37. The measurement of total concentrations in aqueous humor is appropriate.

2.3.3. What bioanalytical methods are used to assess concentrations?

In the pharmacokinetic studies conducted by the Applicant (C-05-43, C-05-23, C-06-37), aqueous humor concentrations of dexamethasone were measured after ocular administration of tobramycin 0.3%/dexamethasone X% (X = 0.025, 0.033, 0.05) or TobraDex® by an HPLC tandem mass spectrometry (HPLC/MS/MS) method developed at Alcon, and validated at both Alcon (C-05-43) and ———— (C-05-23, C-06-37). b(4)

2.3.3.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The range of the standard curve is 1.00 to 200 ng/mL for dexamethasone in human aqueous humor. Overall, reported dexamethasone concentrations in aqueous humor ranged between 2.07 to 128 ng/mL in Study C-06-37. Standard curves were obtained by linear least squares regression analysis, with (1/x) weighting. The range of the assay was sufficient to measure dexamethasone concentrations in aqueous humor for the intended purpose.

2.3.3.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The lower limit of quantitation (LLOQ) of dexamethasone in aqueous humor was 1.00 ng/mL, and the upper limit of quantitation (ULOQ) was 200 ng/mL.

2.3.3.3. What are the accuracy, precision, and selectivity at these limits?

A summary of accuracy and precision of calibration standards for the dexamethasone assay are presented in Table 2.3.3.3-1. A summary of accuracy and precision for quality control samples are presented in Table 2.3.3.3-2. The procedure was fully validated for the working range of 1.00 to 200 ng/mL for dexamethasone in human aqueous humor.

Table 2.3.3.3-1 Calibration Standards Accuracy and Precision for Dexamethasone in Aqueous Humor

	Alcon* (range)	——— ** (range)
Intra-Day		
Accuracy (%)	94.0 - 105	96.8 – 103
Precision (% RSD)	3.93 – 10.4	2.28 – 9.63
Inter-Day		
Accuracy (%)	96.0 – 106	97.7 – 101
Precision (% RSD)	3.55 – 6.93	2.03 – 10.7

b(4)

*Alcon conducted assay validation for Alcon Study C-05-43

——— conducted assay validation for Alcon Studies C-05-23 and C-06-37 b(4)

Source: 2.7 Clinical Summary, Section 2.7.1

Table 2.3.3.3-2 Quality Control Accuracy and Precision for Dexamethasone in Aqueous Humor

	Alcon* (range)			——— ** (range)		
	Low (3.00 ng/mL)	Medium (95.0 ng/mL)	High (170 ng/mL)	Low (3.00 ng/mL)	Medium (95.0 ng/mL)	High (170 ng/mL)
Intra-Day						
Mean	2.96	88.1	158	3.14	101	184
SD	0.126	3.34	13.8	0.156	6.53	10.5
% RSD	4.26	3.79	8.73	4.97	6.47	5.71
Accuracy (%)	98.7	92.7	92.9	105	106	108
N	6	6	6	6	6	6
Inter-Day						
Mean	2.81	90.2	158	3.21	103	180
SD	0.170	5.11	5.72	0.130	4.67	11.3
% RSD	6.04	5.67	3.63	4.05	4.53	6.28
Accuracy (%)	92.9	94.9	92.9	107	108	106
N	6	6	6	6	6	6

b(4)

*Alcon conducted assay validation for Alcon Study C-05-43

——— conducted assay validation for Alcon Studies C-05-23 and C-06-37 b(4)

Source: 2.7 Clinical Summary, Section 2.7.1

Selectivity against endogenous interferences was demonstrated using control aqueous humor from 10 individual donors. There were no endogenous substances that interfered with the detection and quantitation of dexamethasone, including tobramycin and concomitant medications, prednisolone and fluticasone, which were administered to some patients during the clinical studies.

The accuracy, precision and selectivity of the bioanalytical method are acceptable.

2.3.3.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Stability of dexamethasone in human aqueous humor was demonstrated through at least three freeze/thaw cycles and up to at least 72 hours at room temperature. Long-term frozen storage stability of dexamethasone in aqueous humor was demonstrated for a minimum of 95 days at -20°C and 131 days at -70°C.

2.3.3.5. What is the QC sample plan?

Each run contained QC samples at four levels performed at least in duplicate. One run contained N=6 QCs at each concentration to assess intra-day accuracy and precision assessment. For run acceptance, at least two-thirds of QCs had to assay within ± 15% of nominal with at least one QC at each concentration meeting this criterion. In addition to validation QCs prepared and analyzed at ' ——— additional QCs at 3.00, 95.0 and 170 ng/mL nominal concentrations were prepared and qualified at Alcon Research, Ltd. and sent to ' ——— for duplicate analysis. All Alcon QCs met acceptance criteria. b(4)

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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

4. APPENDICES

4.1. Individual Study Reviews

4.1.1. Study C-06-37

TITLE:
A Double-Masked, Parallel Group, Randomized, Single-Dose Bioequivalence Study of Tobradex AF Suspension and TOBRADEX Ophthalmic Suspension

Date(s): 27NOV2006 to 22FEB2007

Principal Investigator: Robert Lehmann, MD; Lehmann Eye Center

OBJECTIVES:
To assess the bioequivalence of Tobradex AF suspension and TOBRADEX by measuring concentrations of dexamethasone in the aqueous humor of cataract surgery patients following a single topical ocular administration.

STUDY DESIGN:
This study was a multi-center, double-masked, parallel-group, randomized, single-dose study to evaluate the bioequivalence of tobramycin 0.3%/dexamethasone 0.05% (Tobradex AF) and TOBRADEX by measuring concentrations of dexamethasone in the aqueous humor of cataract surgery patients following a single topical ocular dose of the tobramycin 0.3%/dexamethasone 0.05% (Tobradex AF) formulation or TOBRADEX. Nine hundred eighty-seven (987) male and female patients 18 years of age and older, of any race, who required cataract surgery, were enrolled to be able to collect pharmacokinetic data for 75 patients for each of the assigned 5 post-dose time points per treatment. Screening Visit procedures included a general medical history and ophthalmic exams/assessments of both eyes, and occurred within 6 weeks (42 days) of cataract surgery. Patients who required cataract surgery and who successfully met the entry criteria returned to the clinic on Day 1. On the day of cataract surgery (Day 1), one dose of the assigned test article was instilled in the operative eye, and at the assigned post-dose time point, cataract surgery began. At the start of cataract surgery, approximately 150 µL of aqueous humor was collected. Then cataract surgery proceeded as usual.

FORMULATIONS:
All eligible participants in this study received a single topical ocular dose of Tobramycin 0.3%/ Dexamethasone 0.05% Ophthalmic Suspension or TOBRADEX. The lot and formulation numbers for the two test articles used in this study are presented in Table 4.1.1-1.

Table 4.1.1-1 Test Article Information for Study C-06-37

Test Article	Lot Numbers	Formulation Identification Numbers
Tob 0.3% / Dex 0.05%	06-500836-1	109442
TOBRADEX	06-500809-1	10611

Tob 0.3% / Dex 0.05% = Tobramycin 0.3% / Dexamethasone 0.05% Ophthalmic Suspension
TOBRADEX = Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension

Source: Clinical Study Report C-06-37, Table 9.4.2-1

PHARMACOKINETIC ASSESSMENTS:
Patients were randomized to receive a single topical ocular dose of Tobramycin 0.3%/ Dexamethasone 0.05% or TOBRADEX at a specified time prior to aqueous humor sample collection. After test article administration, one aqueous humor sample was collected from each enrolled patient at the assigned collection time point (i.e., 0.5 hours [± 5 minutes], 1 hour [± 5 minutes], 2 hours [± 10 minutes], 3 hours [± 10 minutes], or 5 hours [± 20 minutes]).

BIOANALYTICAL ANALYSIS:
Aqueous humor concentrations of dexamethasone were determined using a validated HPLC/tandem mass spectrometry (HPLC/MS/MS) assay method with a working range of 1.00 to 200 ng/mL. Sample analysis was completed over 22 runs. Four runs were rejected, two for unacceptable internal standard response, one for analyst error and another due to HPLC instrumentation problems. For run acceptance, at least 75% of the calibration standards had to yield back-calculated concentrations within ±15% of nominal (±20% at the lower limit of quantitation). Each run contained duplicate quality control (QC) samples at each of four different concentrations. At least five of the eight QCs had to assay within ±15% of nominal for run acceptance with at least one QC at each concentration meeting this criterion. A summary of precision and accuracy is presented in Table 4.1.1-2.

Table 4.1.1-2 Inter-Assay QC Results for Dexamethasone in Study C-06-37

	Low (3.00 ng/mL)	Medium 1 (30.0 ng/mL)	Medium 2 (95.0 ng/mL)	High (170 ng/mL)
Mean	2.66	27.9	93.5	164
Std. Dev.	0.189	1.69	5.60	12.2
Accuracy (%)	88.7	93.0	98.4	96.5
RSD (%)	7.11	6.06	5.99	7.44
N	36	36	36	36

Source: Clinical Study Report C-06-37, Appendix Report TDOC-0005882, Table 1-.1

A total of 982 aqueous humor samples were received at Alcon Research, Ltd. Samples were inspected upon receipt and any that had insufficient volume for at least a single assay (<25 µ L) were held at Alcon and not shipped for analysis. A total of 25 samples received at Alcon were not analyzed. Eight of these 25 samples did not meet the minimum volume requirement. One of the eight contained no visible sample and eleven others showed visible contamination with other ocular tissue components. The six additional samples of the 25 not analyzed were received thawed and their storage history and stability could not be verified.

PHARMACOKINETIC/STATISTICAL ANALYSIS:
The primary pharmacokinetic variable was the area under the concentration-time curve up to the last measured concentration (AUC_{0-5}). The pharmacokinetic variable was based on mean aqueous humor drug concentrations of dexamethasone at each of the five sparse sampling time points (0.5, 1, 2, 3 and 5 hours). Area under the concentration-time curve (AUC) was considered the preferred pharmacokinetic parameter for evaluating the systemic exposure of drugs using a sparse sampling model. The primary statistical objective of this study was to demonstrate the bioequivalence of Tobradex AF suspension (tobramycin 0.3%/dexamethasone 0.05%) and TOBRADEX (tobramycin 0.3%/dexamethasone 0.1%). Primary inference was based on the construction of a two-sided 90% confidence interval about the ratio of AUC_{0-5} values. In

addition, the maximal mean concentration (Cmax) and the time point at which the maximal mean concentration was observed (Tmax) were also estimated as secondary pharmacokinetic parameters.

Based on a target $AUC_{0\text{-}5}$ ratio of 1.0, a total of approximately 750 evaluable aqueous humor samples (75 aqueous humor samples collected at each of the five planned sampling time points (0.5, 1, 2, 3, and 5 hours) per treatment group) would provide at least 90% power to reject both the null hypothesis that the ratio of the test mean to the standard mean is below 0.8 and the null hypothesis that the ratio of test mean to the standard mean is above 1.25. Nine hundred eighty-seven patients were enrolled in the study to ensure collection of evaluable pharmacokinetic data for at least 75 patients for each of the 5 post-dose time points per treatment. This sample size estimate was based on the construction of a 90% confidence interval about a target ratio of 1.0 with a lower limit of 0.8 and an upper limit of 1.25, and a two one-sided test procedure with α=0.05 for each test. This sample size estimate was robust against deviations from the hypothesized ratio of 1.0, and provided sufficient power to demonstrate bioequivalence covering a target ratio that ranges from 0.90 to 1.10 and any samples that may not have been evaluable or analyzable. Estimates of variability in previous studies (C-05-43, C-05-23) were used to obtain the above estimates of sample size.

The per protocol results were considered the primary analysis. Dexamethasone concentrations that were below the lower limit of quantitation (1.00 ng/mL) were replaced with one-half the lower limit of quantitation. Additional data analyses utilized imputation methods where BLQ values were analyzed as missing or zero; the results were similar using all three data imputation methods. Data analyses were also performed on the intent-to-treat data set using the three different imputation methods. The results were similar to those observed for the per protocol data set. The Applicant used both the Fieller's method and the bootstrap method to estimate the 90% confidence interval for the ratio of $AUC_{0\text{-}5}$ of the test product versus the reference product for per protocol and intent-to-treat populations.

Additional details regarding the Applicant's statistical analysis and the Office of Biostatistics review can be found in the Section 4.2 of this review.

RESULTS:

Study Population and Disposition

Of the 987 cataract patients enrolled in this study, 4 patients were excluded from all analyses (safety, per protocol, and intent-to-treat [ITT]) because they did not receive test article; 2 patients did not have an aqueous humor sample collected during surgery and therefore no samples were received by the Sponsor. Of the 981 samples received, 24 were not analyzed for the following reasons: an inadequate (< 25 µL) sample volume (N=7); a contaminated sample (N=11); or a thawed sample (N=6). The resulting ITT data set included aqueous humor concentrations of dexamethasone for 957 patients. The per protocol data set included dexamethasone concentrations for 886 patients. In addition to the 30 patients excluded from the ITT analysis, 71 additional patients were excluded from the per protocol data set for the following reasons: sample collected outside of the protocol defined window (N=27), concomitant medications administered within 20 minutes of test article dosing (N=9), excluded concomitant disease (N=26), administration of excluded concomitant medication (N=1), dosing with the wrong test article (N=4), issues with test article dosing (N=2), unconfirmed sample collection time (N=1), and possible sample contamination with vitreous (N=1).

Reviewer Comment: Based on the information provided in Clinical Study Report C-06-37, the exclusions of data due to protocol deviations were appropriate.

Demographics

A summary of demographic and baseline characteristics for the study population is presented in Table 4.1.1-3. There were no statistically significant or clinically relevant differences between groups for any of the demographic characteristics. There were no statistically significant or clinically relevant differences in any of the demographic characteristics for the per protocol and intent-to-treat populations.

Table 4.1.1-3. Demographics and Baseline Characteristics – Study C-06-37

			Treatment				
	Total		Tob 0.3% / Dex 0.05%		TOBRADEX		
	N	%	N	%	N	%	p-value
Age (years)							
18 to 64 years	244	24.8	122	24.9	122	24.7	0.9562
≥65 years	739	75.2	368	75.1	371	75.3	
Sex							
Male	460	46.8	225	45.9	235	47.7	0.5827
Female	523	53.2	265	54.1	258	52.3	
Race							
White	921	93.7	455	92.9	466	94.5	0.6834
Black or African American	41	4.2	24	4.9	17	3.4	
Asian	15	1.5	8	1.6	7	1.4	
American Indian or Alaska Native	1	0.1	0	0.0	1	0.2	
Other	5	0.5	3	0.6	2	0.4	
Ethnicity							
Hispanic, Latino, or Spanish	82	8.3	46	9.4	36	7.3	0.2371
Not Hispanic, Latino, or Spanish	901	91.7	444	90.6	457	92.7	
Iris Color							
Brown	380	38.7	188	38.4	192	38.9	0.9200
Hazel	176	17.9	86	17.6	90	18.3	
Green	60	6.1	33	6.7	27	5.5	
Blue	345	35.1	171	34.9	174	35.3	
Grey	22	2.2	12	2.4	10	2.0	

p-value from chi-square test of independence (Fisher's exact test when expected cell frequencies have N<5)
Tob 0.3% / Dex 0.05% = Tobramycin 0.3% / Dexamethasone 0.05% Ophthalmic Suspension
TOBRADEX = Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension

Source: Clinical Study Report C-06-37, Table 11.2.1.1-1.

Data Sets analyzed

In accordance with the analysis plan, the intent-to-treat analysis was performed on samples collected outside the time window specified in the clinical protocol. Therefore, time points were reassigned to the closest nominal time point of actual sample collection. The per protocol analysis was performed only on samples collected within the protocol defined window for the assigned randomized time point. The number of aqueous humor samples, by time point, included in the intent-to-treat and per protocol analyses are presented in Table 4.1.1-4.

Table 4.1.1-4. Number of Pharmacokinetic Samples Analyzed – Study C-06-37

Treatment Assignment	Time Point Assignment	Intent-to-Treat Analysis (N)*	Per Protocol Analysis (N)**
Tob 0.3% / Dex 0.05%	0.5 Hours	98	91
	1 Hour	94	85
	2 Hours	96	91
	3 Hours	97	86
	5 Hours	95	88
TOBRADEX	0.5 Hours	94	87
	1 Hour	98	90
	2 Hours	97	92
	3 Hours	96	90
	5 Hours	92	86

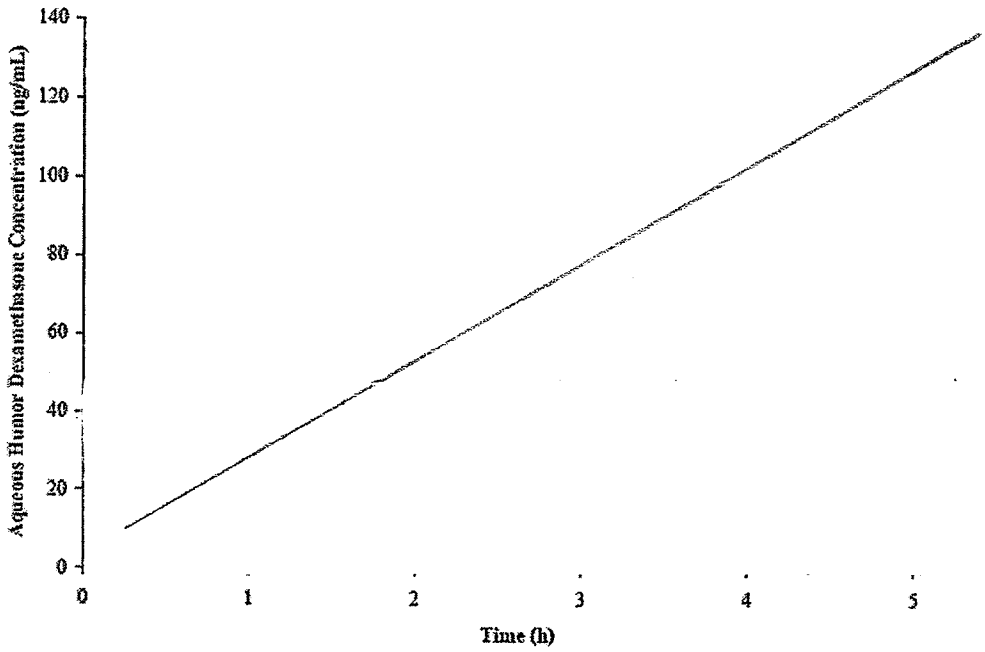
Tob 0.3% / Dex 0.05% = Tobramycin 0.3% / Dexamethasone 0.05% Ophthalmic Suspension
TOBRADEX = Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension
*Closest nominal time point to actual sample collection
**Actual randomized time point

Source: Clinical Study Report C-06-37, Table 11.1.1-1.

Pharmacokinetic Results

Individual and mean aqueous humor concentrations of dexamethasone following administration of Test Product (tobramycin 0.3%/dexamethasone 0.05% ophthalmic suspension) and Reference Product (TOBRADEX; tobramycin 0.3%/dexamethasone 0.1% ophthalmic suspension) are displayed in Figures 4.1.1-1 and Figures 4.1.1-2, respectively. Aqueous humor concentrations of dexamethasone following administration of Test Product (tobramycin 0.3%/dexamethasone 0.05% ophthalmic suspension) and Reference Product (TOBRADEX; tobramycin 0.3%/dexamethasone 0.1% ophthalmic suspension) are summarized descriptively in Table 4.1.1-5. Ratios of mean dexamethasone concentrations at each time point are presented in Figure 4.1.1-3 and Table 4.1.1-6. Mean dexamethasone concentrations at each time point were comparable for the two formulations. The range in dexamethasone aqueous humor levels at each sampling time was similar between the tobramycin 0.3% / dexamethasone 0.05% ophthalmic suspension and TOBRADEX treatment groups; the variability (SD) of the dexamethasone concentrations at each sampling time was not markedly different between the two formulations. The maximal mean concentration of dexamethasone (Cmax) was observed at 2 hours for both treatment groups. Mean dexamethasone concentrations at each time point were comparable for the two formulations as indicated by the ratios of mean dexamethasone concentrations (tobramycin 0.3% / dexamethasone 0.05% to TOBRADEX). Descriptive statistics of the dexamethasone aqueous humor concentrations for the intent-to-treat data set were similar. The ratios of mean dexamethasone concentrations across time points for both formulations fell between 0.80 and 1.25 with values ranging from 0.899 to 1.1; similar results were observed for the mean ratios of the intent-to-treat data.

Figure 4.1.1-1. Individual Dexamethasone Aqueous Humor Concentrations Versus Time from Cataract Patients Following a Single Unilateral Topical Ocular Dose of Tobramycin 0.3%/Dexamethasone 0.05% or TOBRADEX (Per Protocol Analysis)



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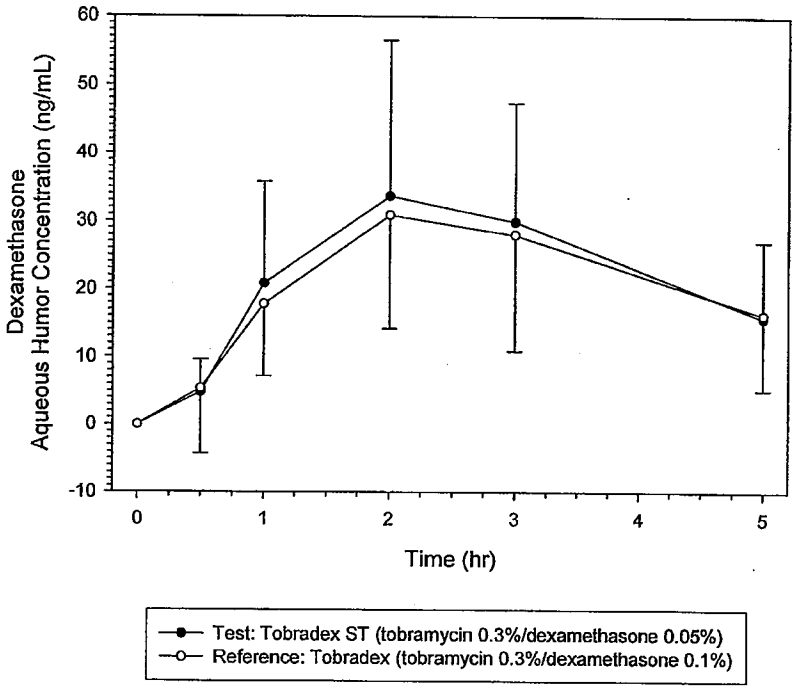
Tob 0.3% / Dex 0.05% = Tobramycin 0.3% / Dexamethasone 0.05% Ophthalmic Suspension
TOBRADEX = Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension
*Actual randomized times staggered for presentation purposes
BLQ values replaced with one-half the limit of quantitation

Source: Clinical Study Report C-05-37, Figure 11.4.1.1-1.

Figure 4.1.1-2. Mean Dexamethasone Aqueous Humor Concentrations Versus Time from Cataract Patients Following a Single Unilateral Topical Ocular Dose of Tobramycin 0.3%/Dexamethasone 0.05% or TOBRADEX (Per Protocol Analysis)



Source: Clinical Study Report C-06-37, Table 11.4.1.1-1.

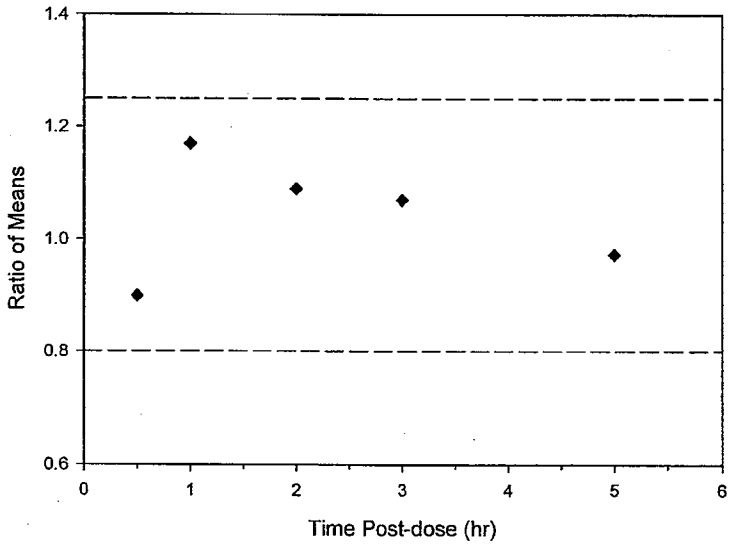
Table 4.1.1-5. Descriptive Statistics for Dexamethasone Aqueous Humor Concentrations from Cataract Patients Following a Single Unilateral Topical Ocular Dose of Tobramycin 0.3%/Dexamethasone 0.05% or TOBRADEX (Per Protocol Analysis)

		Dexamethasone Concentration (ng/mL)					
Treatment	Time Point*	Mean	Median	SD	N	Min	Max
Tob 0.3% / Dex 0.05%	30 Minutes	4.79	3.06	4.84	91	BLQ	32.9
	1 Hour	20.8	17.7	15.0	85	BLQ	78.8
	2 Hours	33.7	29.8	22.8	91	3.31	128
	3 Hours	29.9	25.6	17.4	86	5.30	87.6
	5 Hours	15.8	13.1	11.2	88	2.07	56.2
TOBRADEX	30 Minutes	5.33	3.05	9.64	87	BLQ	78.7
	1 Hour	17.8	16.3	10.6	90	BLQ	49.1
	2 Hours	30.9	29.3	16.7	92	4.07	97.4
	3 Hours	28.0	24.7	17.1	90	2.73	84.1
	5 Hours	16.3	13.6	11.1	86	2.74	57.3

Tob 0.3% / Dex 0.05% = Tobramycin 0.3% / Dexamethasone 0.05% Ophthalmic Suspension
TOBRADEX = Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension
*Actual randomized time point
BLQ = Below the limit of quantitation (<1.00 ng/mL)
BLQ values replaced with one-half the limit of quantitation

Source: Clinical Study Report C-06-37, Table 11.4.1.1-1.

Figure 4.1.1-3. Ratios of Dexamethasone Mean Concentrations for Tobramycin 0.3%/Dexamethasone 0.05% or TOBRADEX per Time Point (Per Protocol Analysis)



Source: Clinical Study Report C-05-37, Figure 11.4.1.1-2.

Table 4.1.1-6. Mean Dexamethasone Concentrations and Corresponding Ratios for Tobramycin 0.3%/Dexamethasone 0.05% to TOBRADEX Per Time Point (Per Protocol Analysis)

Time Point*	Tob 0.3% / Dex 0.05% Mean Conc. (ng/mL)	TOBRADEX Mean Conc. (ng/mL)	Mean Conc. Ratio
30 Minutes	4.79	5.33	0.899
1 Hour	20.8	17.8	1.17
2 Hours	33.7	30.9	1.09
3 Hours	29.9	28.0	1.07
5 Hours	15.8	16.3	0.973

Tob 0.3% / Dex 0.05% = Tobramycin 0.3% / Dexamethasone 0.05% Ophthalmic Suspension
TOBRADEX = Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension
*Actual randomized time point
BLQ values replaced with one-half the limit of quantitation

Source: Clinical Study Report C-06-37, Figure 11.4.1.1-2.

Sparse sampling pharmacokinetic parameters for both treatment groups are shown in Table 4.1.1-7. The maximal mean concentration (Cmax) reached at 2 hours post-dose for both treatment groups, was 33.7 ng/mL and 30.9 ng/mL for tobramycin 0.3%/dexamethasone 0.05% and TOBRADEX, respectively. Similarly, the sparse sampling $AUC_{0\text{-}5}$ was slightly higher for tobramycin 0.3%/dexamethasone 0.05% (112 ng·hr/mL) than for TOBRADEX (105 ng·hr/mL). $AUC_{0\text{-}5}$ and Cmax values from the intent-to-treat analysis were comparable to those from the per protocol analysis.

Table 4.1.1-7. Sparse Sampling Pharmacokinetic Parameters for Tobramycin 0.3%/Dexamethasone 0.05% to TOBRADEX Per Time Point (Per Protocol Analysis)

			AUC Estimates (ng*hr/mL)			
Treatment	Mean Conc. at T_{max} † (ng/mL)	T_{max} (h)	AUC*	SE	Lower 95% CL	Upper 95% CL
Tob 0.3% / Dex 0.05%	33.7	2.00	112	4.08	104	120
TOBRADEX	30.9	2.00	105	3.57	98.2	112

Tob 0.3% / Dex 0.05% = Tobramycin 0.3% / Dexamethasone 0.05% Ophthalmic Suspension
TOBRADEX = Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension
† The time point with the maximum mean concentration was defined as T_{max} and the mean concentration at that time point was considered C_{max}
*A mean concentration of 0 ng/mL was imputed at time 0 for each treatment group to obtain the estimates of $AUC_{0\text{-}5}$
BLQ values replaced with one-half the limit of quantitation

Source: Clinical Study Report C-06-37, Table 11.4.1.1-3.

The results of the bioequivalence calculations for the primary parameter for comparison (AUC_{0-5}) for various analysis methods are summarized in Table 4.1.1-8. The ratio of the AUC_{0-5} values (tobramycin 0.3%/dexamethasone 0.05% [Test] to TOBRADEX [Reference]) was 1.07, with lower and upper 90% confidence limits of 0.983 and 1.16, respectively. Results were similar for both analyses and analysis populations.

Table 4.1.1-8. 90% Confidence Intervals Surrounding the Ratio of Dexamethasone AUC Values for Tobramycin 0.3%/Dexamethasone 0.05% to TOBRADEX (Per Protocol with BLQ Replaced with One-Half the Limit of Quantitation)

Analysis Method	*Dexamethasone AUC_{0-5}*			*90% CI*	
	Test	*Reference*	*Ratio*	*Lower Bound*	*Upper Bound*
Fieller's (per protocol)	112	105	1.07	0.983	1.16
Fieller's (ITT)	113	104	1.09	1.01	1.18
Bootstrap (per protocol)	112	105	1.07	0.996	1.19
Bootstrap (ITT)	113	104	1.09	1.01	1.20

Source: Clinical Study Report C-06-37, Section 14.2.1.3.

The ratio of Cmax values was determined as a secondary parameter of relative aqueous humor exposure between tobramycin 0.3%/dexamethasone 0.05% and TOBRADEX. The mean Cmax was observed at 2 hours for both formulations and is comparable as reflected by a ratio of 1.09; similar results were observed for the intent-to-treat data set.

In summary, the 90% confidence interval (0.983, 1.16) around the ratio (1.07) of the aqueous humor dexamethasone AUC_{0-5} values for tobramycin 0.3% / dexamethasone 0.05% ophthalmic suspension and TOBRADEX® (tobramycin 0.3% / dexamethasone 0.1%) were within 0.80 to 1.25, demonstrating that the two formulations are bioequivalent.

Safety Results

The safety of tobramycin 0.3% / dexamethasone 0.05% and TOBRADEX was evaluated in 983 adult and elderly patients who were randomized into the study and received the single administration of study drug. No deaths were reported during the study. One serious adverse event (hospitalization due to sinus tachycardia), assessed to be unrelated to the use of study drug, was reported in a patient with exposure to tobramycin 0.3% / dexamethasone 0.05%. No patients were discontinued from the study due to adverse events. One treatment-related adverse event (stinging eye coded to eye pain) was reported in a patient with exposure to TOBRADEX. All other adverse events were assessed to be unrelated to the use of study drug. The most frequently reported overall adverse event (related and not related combined) in the tobramycin 0.3% / dexamethasone 0.05% group was increased blood pressure (an incidence of 0.6%), with procedural complication (vitreous prolapse, capsular tear) the most frequently reported adverse event in the TOBRADEX group (an incidence of 0.4%). The Applicant concluded while definitive safety conclusions cannot be made due to the limited duration of drug exposure in this study, no safety issues were identified in the overall safety population based upon a review of adverse events.

APPLICANT'S CONCLUSIONS:
The current study was designed to demonstrate bioequivalence of dexamethasone aqueous humor exposure for the marketed product, TOBRADEX, and tobramycin 0.3%/dexamethasone 0.05% ophthalmic suspension. The ratio of the AUC values (tobramycin 0.3%/dexamethasone 0.05% to TOBRADEX) was determined for the per protocol (1.07) and the intent-to-treat data sets (1.09). The 90% confidence interval around the ratio of the AUC values for both the per protocol and intent-to-treat analyses fell within the required boundaries (0.80 – 1.25) to demonstrate bioequivalence of the two formulations.

No safety issues were identified in patients administered a single dose of tobramycin 0.3%/ dexamethasone 0.05% or TOBRADEX prior to cataract surgery based upon a review of adverse events, which included an assessment of incidence, seriousness (serious/nonserious), treatment relatedness, rate of patient discontinuation due to adverse events, and individual adverse event characteristics. Further, the tobramycin 0.3%/dexamethasone 0.05% and TOBRADEX treatment groups exhibited similar safety profiles based upon this analysis of safety. Definitive safety conclusions cannot be made due to the limited duration of exposure to tobramycin 0.3%/dexamethasone 0.05% in this study. However, the long-term safety following multiple dosing of the reference product, TOBRADEX, has been well-established and since bioequivalence of the two formulations has been demonstrated in this study, the comparative safety profile of the products following long-term exposure should be similar.

REVIEWER ASSESSMENT:
Results from Study C-06-37 adequately assessed the equivalence of Tobradex AF ophthalmic suspension (tobramycin 0.3%/dexamethasone 0.05%) and TOBRADEX by measuring concentrations of dexamethasone in the aqueous humor of cataract surgery patients following a single topical ocular administration. The Applicant's equivalence conclusions based on the primary pharmacokinetic parameter $AUC_{0\text{-}5}$ are valid. For further assessment of the Applicant's statistical analysis, see Section 4.2.

4.1.2. Study C-99-33

TITLE:
Plasma Levels of Tobramycin and Dexamethasone Following Topical Dosing with TobraDex® Eye Drops in Healthy Volunteers

Date(s): 11JUL2000 to 14JUL2000

Principal Investigator: Dr. Salvatore Febbraro; Simbec Research Ltd.

OBJECTIVES:
To evaluate the pharmacokinetics of tobramycin and dexamethsone following multiple ocular bilateral administration with TobraDex® Eye Drops in healthy volunteers.

STUDY DESIGN:
This study was a single-center, open-label, multiple-dose study to evaluate the pharmacokinetics of tobramycin and dexamethsone following QID ocular bilateral administration with TobraDex® Eye Drops in healthy male and female volunteers. Twelve (12) healthy male and female subjects 18 years of age and older were enrolled. Subjects meeting all qualifying criteria upon Screening were administered TobraDex® Eye Drops on Day 1. One drop of study medication was instilled into each eye four times daily for two consecutive days.

FORMULATIONS:
Study participants received multiple topical ocular doses of TobraDex® Eye Drops (Tobramycin 0.3%, Dexamethasone 0.1%). The lot number for the test article used in this study was 99-600009-1.

PHARMACOKINETIC ASSESSMENTS:
Blood samples for the determination of plasma drug concentrations of tobramycin and dexamethasone were taken at a total of fifteen time points for each subject, as follows: 0 (pre-dose), 0.5, 1, 1.5, 2, 4 and 6 hr after the first dose on Day 1; and pre-dose (Dose 8), 0.5, 1, 1.5, 2, 4, 6 and 8 hr after the last dose on Day 2.

BIOANALYTICAL ANALYSIS:

Dexamethasone
Dexamethasone plasma concentrations were determined using a validated high performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) method. Plasma was spiked with ———— as internal standard. Standard curves were obtained by weighted linear regression analysis, with $1/x^2$ weighting. The range of calibrations standards was 5.00 to 5,000 pg/mL and for quality controls, 10.0 to 4,000 pg/mL. b(4)

One hundred eighty (180) duplicate samples were received frozen on dry ice and stored at -70°C until analyzed. All reported dexamethasone concentrations came from analytical runs which passed acceptance criteria. Back-calculated calibration standard inter-day accuracy ranged from 96.3 to 103% of nominal. Inter-day precision of calibration standards ranged from 4.27 to 10.4% RSD. QC samples analyzed with production runs showed an inter-day accuracy ranging from 90.6 to 96.1% of nominal with inter-day precision ranging from 4.24 to 16.9% (at the LLOQ) RSD.

Day 1 pre-dose samples for four of the twelve subjects showed signals corresponding to quantifiable concentrations of dexamethasone. In two cases (Subjects 2 and 5) the levels were very close to the 5.00 pg/mL quantitation limit. In the other two cases the levels were significantly higher (339 and 211 pg/mL for Subjects 3 and 6, respectively). These four samples had shown similar levels of response on a previous run which did not meet acceptance criteria due to QC failure. Instrument carryover was ruled out as a potential cause, based on plasma blanks analyzed in the same run from which the anomalous reported values came. The cause of this apparently measurable dexamethasone signal in four samples which should have not had drug present is unknown.

Of the forty-one samples subjected to repeat analysis, the repeats confirmed the original value in thirty-one cases while the mean of the repeat and initial assays were reported for eight of the samples. The remaining two repeated samples had had poor agreement between the initial and repeat assays and were therefore reported as "NR" (Not Reportable).

Tobramycin

Tobramycin analysis was performed using a validated competitive enzyme immunoassay (EIA). Each sample was analyzed in triplicate and the mean of the replicates reported to three significant figures. A separate 96 well plate containing replicate samples, standards and QC samples was prepared for each subject. Details regarding assay methodology are presented in Table 4.1.2-1.

Table 4.1.2-1. Summary of Tobramycin Enzyme-Linked Immunoassay Method Utilized in Study C-99-33

Standard:	Tobramycin (lot# 4MS34A)
Standard Curve Concentrations:	100 ng/mL, 50 ng/mL, 25 ng/mL, 12.5 ng/mL, 6.25 ng/mL, 3.12 ng/mL, 1.56 ng/mL, 0.78 ng/mL Tobramycin
Standard Matrix	Ten percent human EDTA plasma
Standard Acceptance Range:	The %CV for each concentration must be ≤ 25% and have a %Nominal value within 30%.
Target Quality Control Sample Concentrations:	High-2, 500 ng/mL; High, 50 ng/mL; Medium, 20 ng/mL; Low, 10 ng/mL; Low-2, 5 ng/mL Tobramycin
Quality Control Acceptance Range:	The %CV for multiple measurements of a QC sample must be ≤ 25%.
Quantitative Range:	0.78 – 100 ng/mL

Source: Technical Report 036:33:0601

The initial run for Subject 12 failed acceptance criteria. However, the second run passed. Also, three individual samples (one from Subject 4 and two from Subject 9) had to be repeated in two separate runs. A total of 180 study samples were analyzed with only 16 samples having quantifiable tobramycin concentrations ranging from 116.1 to 246.8 ng/mL. The remaining 164 samples were below the limit of quantitation with the lower limit of quantitation ranging for 62.5 to 250 ng/mL, depending upon the calibration standard response characteristics of a given plate. Precision and accuracy for calibration curves ranged between 3.4 to 27.5% RSD and 73.7 to 133.6%, respectively. Precision and accuracy for quality controls ranged between 1.3 to 24.7% RSD and 50.1 to 151.5%, respectively.

PHARMACOKINETIC/STATISTICAL ANALYSIS:

Pharmacokinetic parameters for dexamethasone were estimated from plasma concentration-time data using model-independent methods. Due to limited quantifiable plasma data for tobramycin, Cmax and Tmax could only be calculated for 3 subjects.

RESULTS:

Study Population and Disposition

A total of twenty-two (22) subjects were screened, and twelve (12) healthy subjects (6 males and 6 females) were enrolled. All twelve subjects completed the study and were evaluable for safety and pharmacokinetic analysis.

Demographics

A summary of demographic and baseline characteristics for the study population is presented in Table 4.1.1-2.

Table 4.1.2-2. Demographics and Baseline Characteristics – Study C-99-33

Demographic Characteristic	Mean ± SD (Range)
Age (yr)	28 ± 6.8 (22 – 43)
Sex N (%)	6 Male (50.0%) 6 Female (50.0%)
Race N (%)	11 Caucasian (91.7%) 1 Asian (8.3%)
Height (cm)	168 ± 7.1 (158 – 181)
Weight (kg)	69.4 ± 10.0 (51.8 – 83.8)

Source: Clinical Study Report C-99-33, Table 14.

Pharmacokinetic Results

Tobramycin

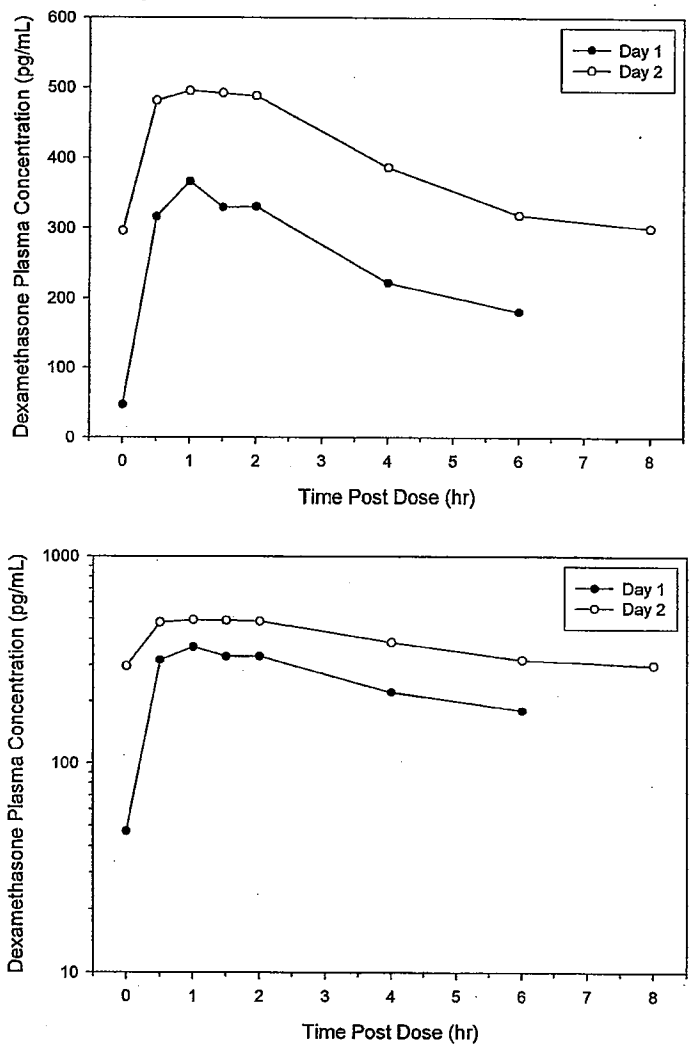
Plasma concentrations of tobramycin were below the limit of quantitation at all time points in 9 of the 12 subjects following QID ocular bilateral administration of TobraDex® (concentrations ranged across subjects from 62.5-250 ng/mL). In the three subjects with quantifiable tobramycin concentrations in plasma, peak plasma concentrations ranging from 124 to 247 ng/mL were observed at 1.5 hours post-dose. Following the last topical bilateral ocular dose on Day 2, quantifiable plasma tobramycin concentrations were observed in 2 of the 3 subjects who had measurable plasma concentrations after the first dose. Cmax values in these two subjects were 147 and 198 ng/mL, respectively, and these values were not greatly different from those observed on Day 1. The limited number of quantifiable tobramycin plasma concentrations following single and multiple topical ocular dosing of TobraDex® did not permit determination of tobramycin AUC or half-life in any of the subjects.

Dexamethasone

Mean (SD) dexamethasone plasma concentration-time profile following QID ocular bilateral administration of TobraDex® in healthy subjects is displayed in Figure 4.1.2-1. Plasma concentrations of dexamethasone were in the picogram per mL range in all subjects following QID ocular bilateral administration of TobraDex®. Dexamethasone was measurable in the plasma samples obtained prior to the first dose on Day 1 in four of the 12 subjects. The reason for this cannot be readily explained since the analytical results were confirmed and inspection of the subject study records and medical history indicate no concomitant medications or other apparent reasons for these measurable pre-dose samples. For the two subjects with higher reported pre-

dose concentrations (339 pg/mL for Subject 03 and 211 pg/mL for Subject 06), these data were included in the pharmacokinetic evaluation so that the observed plasma concentrations would represent maximal systemic exposure of dexamethasone in these two subjects.

Figure 4.1.2-1. Mean (SD) Dexamethasone Plasma Concentration-Time Profile Following QID Ocular Bilateral Administration of TobraDex® in Healthy Subjects



Source: Clinical Study Report C-99-33, Appendix A.

Dexamethasone plasma pharmacokinetic parameters following QID ocular bilateral administration of TobraDex® in healthy subjects are summarized descriptively in Table 4.1.2-2. Observed Cmax values on Day 1 ranged from 112 to 809 pg/mL. The time of the observed Cmax values (Tmax) ranged between 0.5 to 2 hours post-dose. Dexamethasone plasma concentrations declined monophasically. Estimated from the terminal plasma data obtained out to 6 hours post-dose, the mean half-life was 4.55 ± 1.80 hours. The mean AUC over the 6 hour dosing interval

was 1538 ± 969 pg·hr/mL. Following the last bilateral topical ocular dose on Day 2, peak plasma concentrations of dexamethasone were higher than those seen after the initial dose in 9 of the 12 subjects indicating some accumulation of dexamethasone in plasma with the QID regimen. The Day 2 Cmax values ranged from 220 to 888 pg/mL. Dexamethasone plasma levels declined monophasically with a mean half-life estimate from the plasma data out to 8 hours post-dose of 10.19 ± 2.97. Estimated half-lives after multiple dosing are generally longer than those values estimated after the first dose in the majority of subjects. The predicted accumulation ratio was approximately 2.9 which is somewhat higher than the observed individual and mean Cmax and AUC ratios for Day 1/Day 2 (1.6 and 2.0, respectively).

Table 4.1.2-2. Descriptive Statistics for Dexamethasone Plasma Pharmacokinetic Parameters Following QID Ocular Bilateral Administration of TobraDex® in Healthy Subjects

		Dose	
Parameter		**First**	**Last**
$AUC_{0\text{-}6}$ (pg•hr/mL)	Mean	1538	2524
	Std	969	981
	N	12	12
	Min	488	974
	Max	3910	4120
$AUC_{0\text{-}inf}$ (pg•hr/mL)	Mean	2217	6630
	Std	1122	3174
	N	11	11
	Min	949	2320
	Max	3920	11700
C_{max} (pg/mL)	Mean	405	555
	Std	199	217
	N	12	12
	Min	112	220
	Max	809	888
T_{max} (hours)	Mean	1.0	1.2
	Std	0.5	0.7
	N	12	12
	Min	0.5	0.5
	Max	2.0	2.0
$T_{½}$ (hours)	Mean	4.55	10.19
	Std	1.80	2.97
	N	11	11
	Min	2.90	6.52
	Max	9.45	15.50
K (1/hours)	Mean	0.168	0.073
	Std	0.048	0.020
	N	11	11
	Min	0.073	0.045
	Max	0.239	0.106

Source: Clinical Study Report C-99-33, Table 9.

APPLICANT'S CONCLUSIONS:
Overall, this topical ocular study of TobraDex® Eye drops demonstrated minimal plasma exposure of tobramycin and dexamethasone following multiple topical ocular doses in healthy male and female subjects.

REVIEWER ASSESSMENT:
Results from Study C-99-33 adequately evaluated the systemic pharmacokinetics of dexamethsone following multiple ocular bilateral administration with TobraDex® Eye Drops in healthy volunteers. The Applicant's conclusions regarding dexamethasone based on this study are acceptable from a Clinical Pharmacology perspective.

Based on review of assay performance results, the immunoassay used to measure tobramycin in plasma was ***inadequate*** for purposes of describing systemic exposure following ocular administration of TobraDex®. The ranges of % accuracy for calibration curves and quality control samples are unacceptable (accuracy ranges: 73.7 to 133.6% and 50.1 to 151.5%, respectively). Statements regarding systemic exposure of tobramycin should not be included in the proposed labeling for TobraDex-ST®.

4.2. Biostatistics Consult

STATISTICAL REVIEW
January 11, 2008

NDA 50-818

Drug Product:	Tobramycin 0.3% and Dexamethasone 0.05%
Sponsor:	Alcon Research, Ltd.
Reference Product:	Tobradex® (Tobramycin 0.3%/Dexamethasone 0.1% Ophthalmic Suspension)
Study Number:	C-06-37
Study Title:	A Double-Masked, Parallel-group, Randomized, Single-Dose Bioequivalence Study of Tobradex AF Suspension and Tobradex Ophthalmic Suspension
OCP Reviewer:	Kimberly Bergman, Pharm. D.
Statistical Reviewer:	Meiyu Shen, Ph.D.

Objectives of the study

The primary objective of this study was to demonstrate that the prednisolone concentration in the aqueous humor, as assayed in this study, for the corticosteroid component of the corticosteroid/antibacterial drug product, Test Product (Dexamethasone 0.05% and Tobramycin 0.3%) ophthalmic suspension) was bioequivalent to the currently marketed corticosteroid, Reference Product (Dexamethasone 0.1% and Tobramycin 0.3%).

Study Design

This was a multi-center, randomized, double-masked, parallel-group, single-dose study to evaluate the bioequivalence of Tob 0.3%/Dex 0.05% and TOBRADEX® by measuring concentrations of dexamethasone in the aqueous humor of cataract surgery patients following a single topical ocular dose of the Tob 0.3% / Dex 0.05% formulation or TOBRADEX. Nine hundred eighty-seven male and female patients 18 years of age and older, of any race, who required cataract surgery, were enrolled to be able to collect pharmacokinetic data for 75 patients for each of the 5 post-dose time points per treatment.

The two treatments are:

- Test Product (Dexamethasone 0.05% and Tobramycin 0.3%) ophthalmic suspension (Lot #: 06-500836-1, Formulation identification #: 109442)
- Reference Product (Dexamethasone 0.1% and Tobramycin 0.3%) ophthalmic suspension (Lot #: 06-500809-1, Formulation identification #: 10611)

Efficacy Evaluations

There was no placebo control treatment in this study. Efficacy evaluation was not performed.

Bioequivalence Evaluation

Sponsor's primary pharmacokinetic variable

The primary pharmacokinetic variable was the area under the concentration-time curve up to the last measured concentration (AUC0-5). The pharmacokinetic variable was estimated from the mean aqueous humor drug concentrations of dexamethasone at each of the five sparse sampling time points (0.5, 1, 2, 3 and 5 hours). The area under the curve was estimated using a method

appropriate for sparse sampling (Nedelman JR, Gibiansky E, Lau DTW. Applying Bailer's method for AUC confidence intervals to sparse sampling. Pharm Res 1995; 12(1):124-128.).

The maximum mean concentration (C_{max}) is estimated directly from the observed concentrations. That is, C_{max}=max expected value $\{C_0, C_1, \ldots, C_k\}$, where subscript k represents the number of sampling time points.

On the basis of the trapezoidal rule, the AUC_{0-t_j}, the area under the concentration time profile from zero to the time, t_j ($0<t_1<t_2<t_3, .., <t_j$), is computed as

$$AUC_{0-t_j} = t_1 * \bar{x}_{t_1} / 2 + \sum_{i=1}^{j-1} (\bar{x}_{t_i} + \bar{x}_{t_{i+1}}) \bullet (t_{i+1} - t_i) / 2 \qquad (1)$$

Let x_{qr} represent the response of the r^{th} individual at the q^{th} sampling time point (q=1,…, k). The sponsor defined the sample mean at time t_k in any given group to be:

$$\bar{x}_q = \frac{1}{n_q} \sum_{r=1}^{n_q} x_{qr}$$

The AUC from time zero to time t_k, denoted by AUC(0-t_k), was approximated by the sponsor by

$$AUC(0-t_k) = \sum_{r=1}^{n_q} c_q \bar{x}_q$$

Where
$$c_q = \begin{cases} \frac{1}{2}\Delta_2 & \text{for q = 1} \\ \frac{1}{2}(\Delta_q) + (\Delta_{q+1}) & \text{for q = 2, ..., k - 1} \\ \frac{1}{2}\Delta_k & \text{for q = k} \end{cases}$$

$$\text{for } \Delta_q = t_q - t_{q-1}, \quad q = 2,..., k$$

(2)

Note that the correct definition for c_q is:

$$c_q = \begin{cases} \frac{1}{2}\Delta_2 & \text{for q = 1} \\ \frac{1}{2}[(\Delta_q) + (\Delta_{q+1})] & \text{for q = 2, ..., k - 1} \\ \frac{1}{2}\Delta_k & \text{for q = k} \end{cases}$$

$$\text{for } \Delta_q = t_q - t_{q-1}, \quad q = 2,..., k$$

We believe the sponsor made a typing error in (2). This is supported by our replication of their results, listed in Table 4.

Measurement time

Aqueous humor samples were obtained using a sparse sampling scheme, whereby the time of sample collection will either be 0.5 hours (±5 min.), 1hour (±5 min.), 2 hours (±10 min.), 3 hours (±10 min.), or 5 hours (±20 min.) following a single pre-operative dose of test article on the day of surgery.

Sponsor's analysis populations

The sponsor's safety population included all patients who received study medication.

The sponsor's Intent-to-Treat (ITT) population included all patients who received study medication, had an aqueous humor sample collected, and for whom adequate pharmacokinetic data were collected and available.

The primary analysis of the ITT data set was based on samples obtained at the closest nominal time of actual sample collection. The sponsor said "for example, if the sample for a planned 30-minute time point is actually taken within 1-hour time window then the sample was analyzed as part of the nominal 1-hour data. If the actual sample time did not fall within one of the protocol time windows, then the sample was analyzed as part of the closest nominal time point. If the sampling time is equidistant between two time points then it was analyzed with the planned time point (or the first of the two if between two time points, neither of which was planned)."

The sponsor's Per Protocol (PP) population included all patients who received study medication, satisfied pre-randomization protocol inclusion/exclusion criteria that were relevant to the assessment of pharmacokinetic parameters, had an aqueous humor sample collected, and for whom adequate pharmacokinetic data were collected and available.

In the per protocol analysis, only data from patients for whom aqueous humor samples were collected within the protocol defined window for their assigned time were included.

Table 1 lists disposition and evaluability of patients. Table 2 presents the number of aqueous humor samples, by time point, included in the intent-to-treat and per protocol analyses. In accordance with the analysis plan, the intent-to-treat analysis was performed on some samples collected outside the time window specified in the clinical protocol (TDOC-0005200). Hence, time points were reassigned to the closest nominal time point of actual sample collection. The per protocol analysis was performed only on samples collected within the protocol defined window for the assigned randomized time point.

Table 1. Disposition and evaluability of patients

		Total number of patients enrolled: 987	
		ITT	PP
Number of patients		957	886
Number of patients excluded	Not receiving test article	2	2
	No aqueous humor sample collected	2	2
	Inadequate sample (<25 µl)	7	7
	Contaminated sample	11	11
	Thawed sample	6	6
	Sample collected outside of defined window		27
	Concomitant medications administered within 20 minutes of test article dosing		9
	Concomitant disease		26
	Concomitant medication		1
	Dosing with wrong test article		4
	Issues with test article dosing		2
	Unconfirmed sample collection time		1
	Possible sample contamination with vitreous		1

Table 2. Number of Pharmacokinetic Samples Analyzed

Treatment Assignment	Time Point Assignment	Intent-to-Treat Analysis (N)*	Per Protocol Analysis (N)**
Tob 0.3% / Dex 0.05%	0.5 Hours	98	91
	1 Hour	94	85
	2 Hours	96	91
	3 Hours	97	86
	5 Hours	95	88
TOBRADEX	0.5 Hours	94	87
	1 Hour	98	90
	2 Hours	97	92
	3 Hours	96	90
	5 Hours	92	86

Tob 0.3% / Dex 0.05% = Tobramycin 0.3% / Dexamethasone 0.05% Ophthalmic Suspension
TOBRADEX = Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension
*Closest nominal time point to actual sample collection
**Actual randomized time point

Sponsor's analysis for primary endpoint

The ratio of $AUC_{0\text{-}5}$ (Tob 0.3% / Dex 0.05% to TOBRADEX®) and the 90% confidence intervals surrounding the ratio (calculated using Fieller's method and Bootstrap method) were determined. The sponsor used the per protocol population for the primary analysis. Dexamethasone concentrations that were below the lower limit of quantitation (1.00 ng/mL) were replaced with one-half the lower limit of quantitation. Additional data analyses utilized imputation methods where BLQ values were analyzed as missing or zero.

Data

Each subject contributed one concentration value. Figure 1 shows the distribution of the dexamethasone concentrations versus time for the PP population and Figure 2 shows those for the dexamethasone concentrations versus time for ITT population.

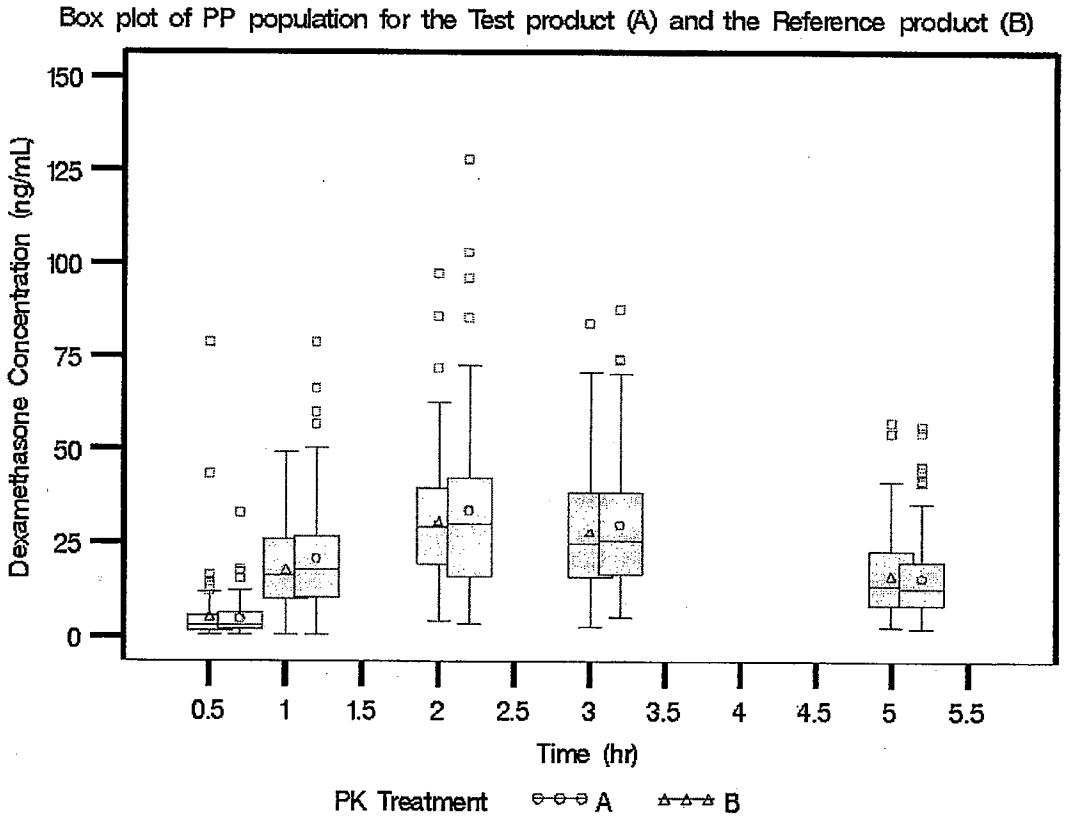


Figure 1. Box plot of concentration versus time for PP population: 0.2 is added to the variable Time of the test product such that two box plots can be displayed side by side.

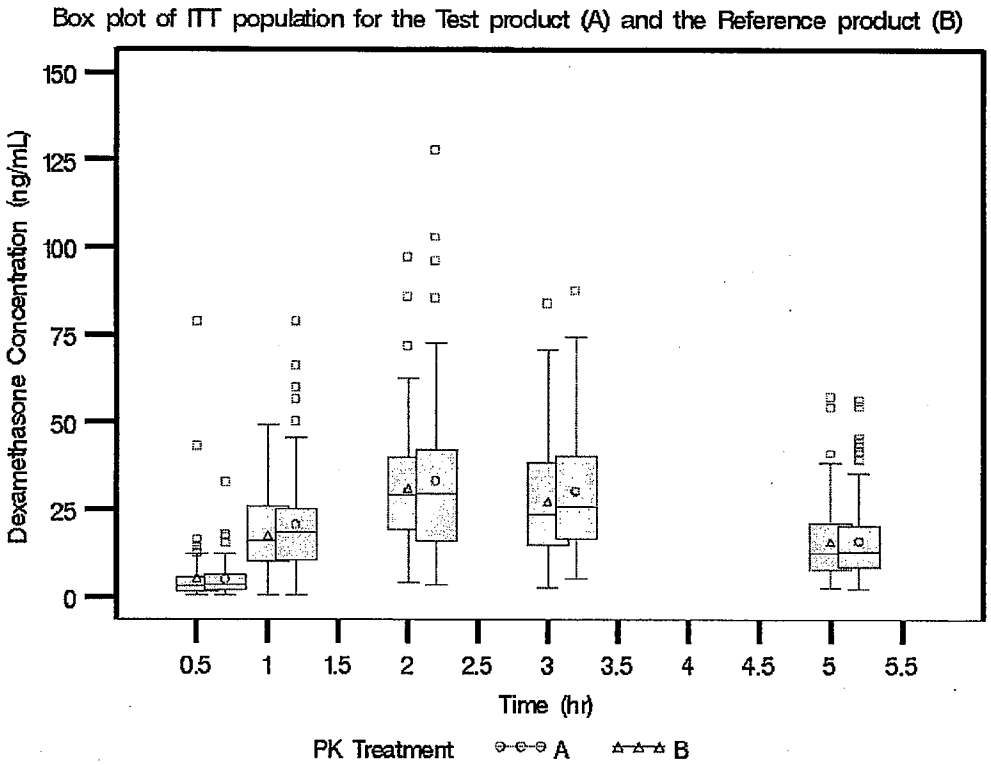


Figure 2. Box plot of concentration versus time for ITT population: 0.2 is added to time for the test product such that two box plots can be displayed side by side.

The sponsor's analysis

The sponsor used both the Fieller's method and the bootstrap method to estimate the 90% confidence interval for the ratio of AUC_{0-5} of the test product versus the reference product for PP and ITT populations.

Table 3. 90% Confidence Intervals Surrounding the Ratio of Dexamethasone AUC_{0-5} Values for Tob 0.3% / Dex 0.05% to TOBRADEX (BLQ Replaced with One-Half the Limit of Quantitation)

Method	Population	5% percentile	Ratio of AUC_{0-5} for test over reference	95% percentile
Fieller's method	PP	0.983	1.07	1.16
Bootstrap	PP	0.996	1.07	1.19
Fieller's method	ITT	1.01	1.09	1.18
Bootstrap	ITT	1.01	1.09	1.20

This statistical reviewer's analysis:

(1) Comparison of the sponsor's AUC and this reviewer's AUC

In order to evaluate the sponsor's equation for calculating AUC, I compared the sponsor's AUC and my calculated AUC in Table 4. The results are identical, and would not have been had Equation (2) been followed. This is why I believe the sponsor did the correct AUC calculation, but made a typing error in (2).

Table 4. Comparison of the sponsor's calculated AUC and this reviewer's calculated AUC for PP population with below the limit of quantitation (BLQ) replaced with one-half the limit of Quantitation

	The sponsor's calculation		This reviewer's calculation	
Treatment	AUC	SE	AUC	SE
Tob 0.3%/Dex 0.05%	112	4.08	112.2	4.08
Tobradex (Tob 0.3%/Dex 0.1%)	105	3.57	105.2	3.57

(2) Bootstrap method

The bootstrap method for estimating 90% confidence interval is illustrated with AUC_{0-5}. To estimate 90% confidence interval for AUC_{0-3}, AUC_{0-2}, and AUC_{0-1}, we followed the same steps.

(a) Estimation of 90% confidence intervals for AUC_{0-5}, AUC_{0-3}, AUC_{0-2}, and AUC_{0-1} via bootstrapping the data from the 886 PP patients, receiving both products and having adequate humor, with replacement

First, bootstrap all 886 PP patients to select 886 with replacement repeatedly 5,000 times.

Second, for each bootstrap sample, compute AUC_{0-5} for the test product and the reference product, separately.

Third, for each bootstrap sample, compute the ratio of AUC_{0-5} for the test product over AUC_{0-5} for the reference product. The 5th percentile and 95th percentile of the ratio of AUC_{0-5} for the test over AUC_{0-5} for reference product comprise the 90% confidence interval.

Fourth, 90% Confidence Intervals for ratio of AUC_{0-5} for the test product and the reference product is obtained as just described in the third step. The results are listed in Table 6.

Table 6. The 90% confidence intervals for ratio of AUC_{0-5}, AUC_{0-3}, AUC_{0-2}, and AUC_{0-1} for the test product versus the reference product (BLQ Replaced with One-Half the Limit of Quantitation)

	Population	5% percentile	Ratio of AUC for test over reference	95% percentile
AUC_{0-5}	PP	0.983	1.069	1.159
AUC_{0-3}	PP	0.997	1.095	1.197
AUC_{0-2}	PP	0.995	1.110	1.235
AUC_{0-1}	PP	0.906	1.079	1.268

This reviewer also calculated the 90% confidence intervals for ratio of AUC_{0-5}, AUC_{0-3}, AUC_{0-2}, and AUC_{0-1} for the test product versus the reference product if BLQ was replaced by missing or by zero. The results listed in the Table 7 are similar among three methods handling BLQ data.

Table 7. The 90% confidence intervals for ratio of AUC_{0-5}, AUC_{0-3}, AUC_{0-2}, and AUC_{0-1} for the test product versus the reference product

	BLQ method	Population	5% percentile	Ratio of AUC for test over reference	95% percentile
AUC_{0-5}	Missing	PP	0.982	1.067	1.159
AUC_{0-3}	Missing	PP	0.998	1.095	1.201
AUC_{0-2}	Missing	PP	0.996	1.110	1.235
AUC_{0-1}	Missing	PP	0.884	1.063	1.251
AUC_{0-5}	Zero	PP	0.981	1.067	1.156
AUC_{0-3}	Zero	PP	0.998	1.095	1.197
AUC_{0-2}	Zero	PP	0.996	1.112	1.232
AUC_{0-1}	Zero	PP	0.904	1.089	1.278

(b). Estimation of 90% confidence intervals for AUC_{0-5}, AUC_{0-3}, AUC_{0-2}, and AUC_{0-1} via bootstrapping the data from the 957 ITT patients, receiving both products and having adequate humor, with replacement

First, bootstrap 957 ITT patients to select 957 with replacement repeatedly 5,000 times.

Repeat Steps 2 to 4 in the above Section (a). The obtained results are listed in Table 8.

Table 8. The 90% confidence intervals for ratio of AUC_{0-5}, AUC_{0-3}, AUC_{0-2}, and AUC_{0-1} for the test product versus the reference product (BLQ Replaced with One-Half the Limit of Quantitation)

	Population	5% percentile	Ratio of AUC for test over reference	95% percentile
AUC_{0-5}	ITT	1.009	1.093	1.182
AUC_{0-3}	ITT	1.010	1.101	1.120
AUC_{0-2}	ITT	1.000	1.112	1.229
AUC_{0-1}	ITT	0.934	1.103	1.285

(3) Fieller's method for the estimation of 90% confidence intervals

The method for estimating 90% confidence interval is illustrated with AUC_{0-5}. To estimate 90% confidence interval for AUC_{0-3}, AUC_{0-2}, and AUC_{0-1}, we repeat the following steps.

First, compute AUC_{0-5} using formula (1) for the test and reference products.

Second, compute the standard error (SE) for each AUC_{0-5}.

Third, using the Fieller's method to compute the 90% confidence interval for the ratio of the (AUC_{0-5}) of the test versus (AUC_{0-5}) of the reference.

Table 9. The 90% confidence intervals for ratio of AUC_{0-5}, AUC_{0-3}, AUC_{0-2}, and AUC_{0-1} for the test product versus the reference product (BLQ Replaced with One-Half the Limit of Quantitation)

Parameter	Population	5% percentile	Ratio of AUC for test over reference	95% percentile
AUC_{0-5}	PP	0.983	1.067	1.158
	ITT	1.008	1.091	1.180
AUC_{0-3}	PP	0.995	1.092	1.197
	ITT	1.005	1.099	1.200
AUC_{0-2}	PP	0.993	1.106	1.230
	ITT	0.999	1.106	1.223
AUC_{0-1}	PP	0.901	1.069	1.274
	ITT	0.929	1.090	1.283

Review Conclusion

- Bootstrap method:
  - 886 PP patients,
    - the 90% confidence limits of the ratios of the test product versus the reference product for AUC_{0-5}, AUC_{0-3}, and AUC_{0-2} for PP population lie in the interval (0.8, 1.25) and the point estimates of the ratios are in the range of (1.069, 1.110) if BLQ was replaced with One-Half the Limit of Quantitation;
    - the 90% confidence limits of the ratios of the test product versus the reference product for AUC_{0-1} do not lie in the interval (0.8, 1.25) and the point estimate of the ratios is 1.079 for the PP population if BLQ was replaced with One-Half the Limit of Quantitation.
    - If BLQ was replaced by missing or by zero, the 90% confidence intervals for ratio of AUC_{0-5}, AUC_{0-3}, AUC_{0-2}, and AUC_{0-1} for the test product versus the reference product are similar to those obtained if BLQ were replaced with One-Half the Limit of Quantitation.

  - 957 ITT patients,
    - the 90% confidence limits of the ratios of the test product versus the reference product for AUC_{0-5}, AUC_{0-3}, and AUC_{0-2} for ITT population lie in the interval (0.8, 1.25) and the point estimates of the ratios are in the range of (1.093, 1.112);
    - the 90% confidence limits of the ratios of the test product versus the reference product for AUC_{0-1} do not lie in the interval (0.8, 1.25) and the point estimate of the ratio is 1.103 for ITT population.

- Fieller's method:
  - 866 PP patients and 957 ITT patients
    - the 90% confidence limits of the ratios of the test product versus the reference product for AUC_{0-5}, AUC_{0-3}, and AUC_{0-2} for PP population as well as for ITT population lie in the interval (0.8, 1.25) and the point estimates of the ratios are in the range of (1.067, 1.106).
    - the 90% confidence limits of the ratios of the test product versus the reference product for AUC_{0-1} do not lie in the interval (0.8, 1.25) and the point estimates of the ratios are 1.069 for PP population, and 1.090 for ITT population.

The results support equivalence of the 2 products for AUC_{0-5}, AUC_{0-3}, and AUC_{0-2}, but not for AUC_{0-1}.

_____
Meiyu Shen, Ph.D.,
Senior Statistical Reviewer, DB VI

Concur: _____
Stella G. Machado, Ph.D.
Director, DBVI

cc:

HFD-880	Kimberly Bergman
HFD-705	Stella G. Machado
HFD-705	Meiyu Shen
HFD-705	DB VI

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/s/

Kimberly Bergman
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