CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	202-514
Submission Date(s):	January 7, 2011
Proposed Brand Name	TBD
Generic Name	Tafluprost
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DTOP
Applicant	MERCK & CO., Inc.
Relevant IND(s)	062690
Submission Type; Code	1S(NME)
Formulation; Strength(s)	Tafluprost 0.0015% Ophthalmic Solution
Indication	For the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension
Dosage and Administration	One drop of Tafluprost 0.0015% ophthalmic solution in the conjunctival sac of the affected eye(s) once daily in the evening

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1. EXECUTIVE SUMMARY

Tafluprost (AFP-168, MK-2452) is an ester prodrug of a new synthetic prostaglandin F2α (PGF2α) analogue selective for the FP prostanoid receptor. Converting in vivo into the pharmacologically active tafluprost acid (AFP-172), tafluprost is a new chemical entity drug product developed for the reduction of elevated intraocular pressure (IOP) in open-angle glaucoma or ocular hypertension. The proposed product, Tafluprost 0.0015% ophthalmic solution (one eye drop once daily), does not contain any preservative agents, such as benzalkonium chloride, which is commonly used in the approved prostaglandin analogues (e.g., Xalatan®, Travatan®, and Lumigan®) for glaucoma treatment and believed to cause potential toxicity due to chronic use. Tafluprost 0.0015% preservative free (PF) and preservative containing (PC) have been approved for reducing of elevated IOP in open angle glaucoma and ocular hypertension in many countries other than the United States.

In support of the NDA, the Applicant submitted clinical studies including:

- Six Phase 1 dose-escalation studies (Studies 74450, 74451, 74452, 74453, 15005, and 77551) to assess the systemic exposure and tolerability of tafluprost ophthalmic solution in healthy subjects.

- Two Phase 2 dose-ranging studies in patients (Studies P15001 and P15002) to support the selection of tafluprost 0.0015% for further development.

- Five Phase 3 studies in patients to assess the efficacy, safety and tolerability of tafluprost for the treatment of glaucoma, including a comparison to latanoprost (Study 74458 [Latanoprost Non-Inferiority Study]), a comparison to timolol (Studies 15003 [Preservative-containing (PC) Tafluprost vs. PC Timolol Non-Inferiority Study] and 001 [Preservative-free (PF) Tafluprost vs. PF Timolol Non-Inferiority Study]), a study examining tafluprost as adjunctive treatment with timolol (Study 74460 [(Adjunctive Treatment to Timolol]), and a bridging study comparing PC and PF formulations of tafluprost (Study 77550 [PF/PC Comparison Study]).

- In addition, an open-label Phase 3b clinical study (77552 [Open label PF tafluprost /latanoprost switch study]) to investigate changes in ocular signs and symptoms when patients were switched from preservative-containing latanoprost to PF tafluprost.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable.

The reviewer's proposed label changes in *Appendix 4.1* will be forwarded to the sponsor.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Tafluprost is an ester prodrug of tafluprost acid, which is further metabolized in vivo via fatty acid β-oxidation and phase II conjugation. The binding of tafluprost acid to human serum albumin (4%) was >99%. Tafluprost acid is not metabolized by major human CYP450 enzymes. It is unknown if tafluprost or tafluprost acid inhibits or induces any CYP450 enzymes. However, given the low systemic exposure (the systemic C_{max} is about $1/9^{th}$ of EC_{50} value) to tafluprost acid following topical ocular administration of tafluprost 0.0015% ophthalmic solution, clinically relevant interactions based on inhibition of CYP450 enzymes are not to be expected for tafluprost and concomitantly administered drugs.

IOP reduction starts about 2 to 4 hours after topical ocular administration and the maximal effect is reached by 12 hours post instillation. The duration of action for tafluprost was greater than 24 hours, which is consistent with the data obtained on other prostaglandin analogues.

Following topical instillation, tafluprost is absorbed through the cornea and is hydrolyzed to the biologically active tafluprost acid (EC_{50} to the recombinant human FP prostanoid receptor = 217 pg/mL, or 0.5 nM). Following 8-day q.d. administration of tafluprost 0.0015% Preservative-free (PF) ophthalmic solution, mean plasma tafluprost acid C_{max} values were 26 pg/mL and 27 pg/mL on Day 1 and Day 8, respectively; mean plasma tafluprost acid AUC values were 394 pg*min/mL and 432 pg*min/mL on Days 1 and 8, respectively (Study 77551). Mean plasma concentrations of tafluprost acid were below the limit of quantification (10 pg/mL) at 30 minutes. Pharmacokinetic parameters (AUC and C_{max}) of the preservative-containing (PC) and PF formulations of tafluprost were comparable.

The effect of the commonly known intrinsic (e.g., renal impairment, hepatic impairment, age gender) and extrinsic (e.g., drug-drug interactions) factors on the PK of tafluprost following topical administration of tafluprost 0.0015% ophthalmic solution has not been studied. Given the low systemic exposure following topical administration, however, dose adjustment is not warranted in patients based on the commonly known intrinsic or extrinsic factors.

2. QUESTION BASED REVIEW

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?

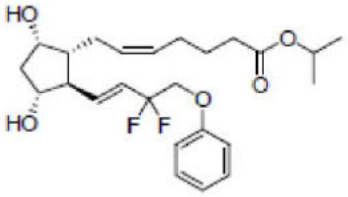
Tafluprost is a colorless to light yellow viscous liquid. It is practically insoluble in water, very soluble in ethanol, diethyl ether, and acetonitrile, sparingly soluble in a mixed solution of phosphate buffer/acetonitrile (1:1).

Structural Formula: $C_{25}H_{34}F_2O_5$

Molecular Weight: 452.53 Dalton

CAS Index Name: 1-methylethyl (5Z)-7-{(1R, 2R, 3R, 5S)-2-[(1E)-3,3-difluoro-4- phenoxy- 1-butenyl]-3,5-dihydroxycyclopentyl}-5-heptenoate

Chemical Structure:



Drug Product:
The drug product, Tafluprost 0.0015% eye drops, is formulated as a sterile, isotonic ophthalmic solution using common excipients and filled (b) (4) into single-dose containers. The solution is clear and colorless with pH of 6.0. The single-dose formulation does not contain benzalkonium chloride (BAC), and the amount of polysorbate 80 is (b) (4). Formulations with preservative BAC, in multidose containers containing 1 to 50 µg/ml tafluprost, were used in most of the clinical studies. **(Table 2.1.1-1)**

Table 2.1.1-1: Composition of the drug product in single-dose and multidose containers

Drug substance	Tafluprost 15 microg/ml eye drops in single-dose container (mg/ml)	Tafluprost 15 microg/ml eye drops in multidose container (mg/ml)
Tafluprost	0.015	0.015
Excipients		
Glycerol	(b) (4)	(b) (4)
Sodium dihydrogen phosphate dihydrate		
Disodium edetate		
(b) (4)		
Polysorbate 80		
Sodium hydroxide and/or Hydrochloric acid		
(b) (4) water (b) (4)		

Two clinical studies (77550 and 77551) were conducted to bridge the formulation differences between the clinical trial formulation (preservative-containing, PC) and the to-be-marketed product (preservative free, PF). The results showed that Tafluprost 0.0015% PF eye drops have similar pharmacokinetic and pharmacodynamic profiles as Tafluprost 0.0015% PC eye drops.

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

Tafluprost is a prodrug of a new synthetic prostaglandin F2α (PGF2α) analogue selective for the FP prostanoid receptor (EC_{50} value of 0.5 nM). The prostaglandins comprise a group of naturally occurring fatty acids which act as autacoids and exert complex physiologic effects by stimulating specific membrane receptors. Like other prostaglandin analogues, tafluprost has also been shown to increase the uveoscleral outflow and decrease IOP in monkeys.

The proposed drug product is indicated for the reduction of elevated IOP in open-angle glaucoma or ocular hypertension.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The recommended dose is one drop of Tafluprost 0.0015% ophthalmic solution in the conjunctival sac of the affected eye(s) once daily in the evening.

2.2. General Clinical Pharmacology

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

The clinical pharmacology studies with tafluprost consisted of pharmacokinetic studies as well as Phase I and Phase II dose-response studies:

- **Pharmacokinetics**: In four Phase 1 dose-escalation studies (74450, 74451, 74452, and 74453), neither tafluprost nor tafluprost acid could be detected when using a bioanalytical method (HPLC/MS/MS) with LLOQ at 0.2 ng/mL (tafluprost) and 0.1 ng/mL (tafluprost acid). One confounding factor is that the plasma samples may have not been stored properly in some of these studies to ensure adequate sample stability. In a subsequent Study 15005, systemic exposure following topical ocular administration of 0.0015% tafluprost ophthalmic solution was successfully assessed using an improved analytical method (HPLC/MS/MS)with LLOQ at 10 pg/mL (tafluprost acid). Furthermore, Study 77551 was conducted to verify if the systemic bioavailability of tafluprost in humans after topical ocular q.d. administration of either tafluprost (0.0015%) PF or PC ophthalmic solution is similar.

- Two Phase 2 **dose-ranging** studies in glaucoma patients were conducted to inform dose selection for Phase 3. In Study P15001, 0.001%, 0.0025%, and 0.005% concentrations of tafluprost were tested. One group of patients received placebo and another received latanoprost (positive control). The IOP reduction- time profiles suggested that the optimal dose of tafluprost is between 0.001% and 0.0025%. In the second Study P15002, the tafluprost concentration was tested at 0.0003%, 0.0015%, and 0.0025%. The study showed that 0.0015% of tafluprost offered the best balance between efficacy (IOP reduction) and tolerability (measured by eye comfort, conjunctival hyperemia, et al).

- **Dose-regimen**: The selected 0.0015% concentration of tafluprost was tested in the Phase II study 74457 (Pilot Latanoprost Comparison Study). This study showed similar efficacy between 0.0015% tafluprost and 0.005% latanoprost. In addition, the duration of action for tafluprost was greater than 24 hours, which is in agreement with the data obtained on other prostaglandin analogues. Hence, similar to latanoprost, a once daily dose regimen is considered appropriate for tafluprost ophthalmic solution.

Based on the Phase II dose-finding and efficacy studies, the optimal balance between efficacy and tolerability with tafluprost administered once daily appeared to be reached at tafluprost 0.0015%. Therefore, this dose regimen was selected for further evaluations in the Phase III clinical studies.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

IOP is accepted as a surrogate endpoint for assessing the efficacy of treatments for open-angle glaucoma and ocular hypertension. The IOP endpoint has served as the basis for approval for all IOP-lowering agents for open-angle glaucoma or ocular hypertension.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

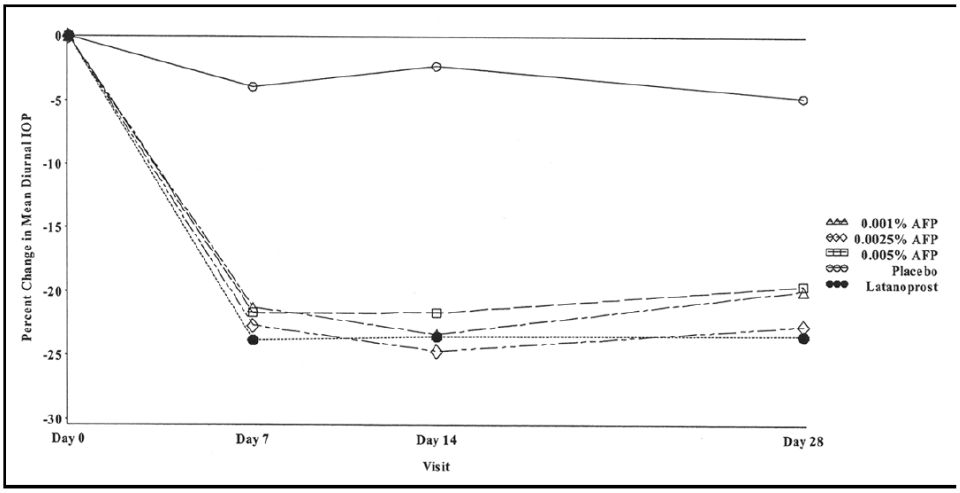
Yes, the sponsor used a validated LC/MS/MS method to quantitate plasma concentrations of the active metabolite, tafluprost acid. (*Refer to Section 2.6*).

2.2.4. Exposure-response

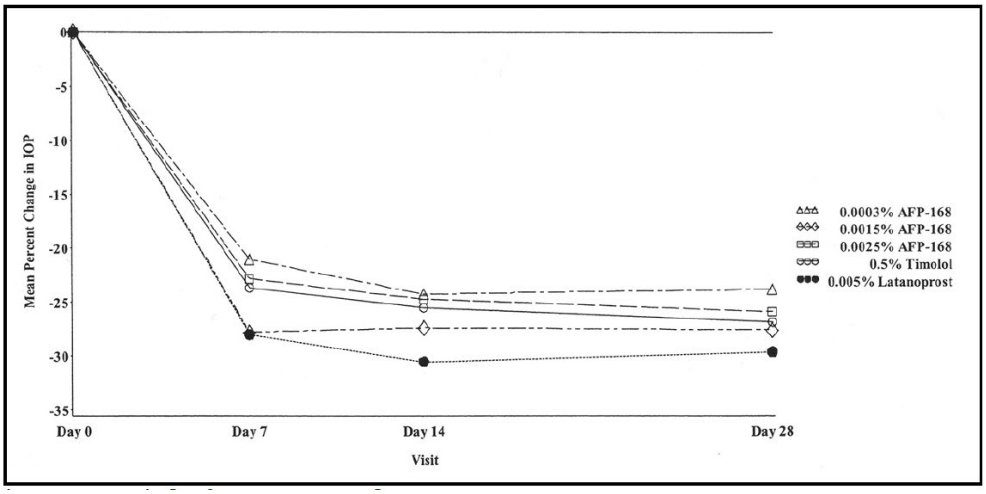
2.2.4.1. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The dose-PD response in the eye was studied in Phase 1 dose escalation studies in healthy subjects and Phase 2 dose-ranging studies in patients. In Phase 2 Study P15001, 0.001%, 0.0025%, and 0.005% concentrations of tafluprost were tested. The IOP reduction- time profiles suggested that the optimal dose of tafluprost is between 0.001% and 0.0025% as a dose higher than 0.0025% did not provide additional IOP reduction (**Figure 2.2.4.1-1**). In the Phase 2 Study P15002, the tafluprost concentrations of 0.0003%, 0.0015%, and 0.0025% were assessed. The study showed that 0.0015% of tafluprost offered the best balance between IOP reduction (**Figure 2.2.4.1-2**) and tolerability (measured by eye comfort, conjunctival hyperemia, et al).

The IOP reduction starts about 2 to 4 hours after administration and the maximal effect is reached 12 hours after instillation. The duration of action for tafluprost was greater than 24 hours, which is in agreement with the data obtained on other prostaglandin analogues.



Source: Study report P15001
Note: IOP was measured at 8 am, 12 pm, 4 pm, and 8 pm on baseline (Day 0) and Days 7, 14, and 28.
Figure 2.2.4.1-1: Percentage Mean Diurnal IOP Reductions During the Treatment Period With Tafluprost Treatment at Different Concentrations of in Study P15001



Source: Study report P15002
Note: IOP was measured at 8 am, 12 pm, 4 pm, and 8 pm on baseline (Day 0) and Days 7, 14, and 28.
Figure 2.2.4.1-2: Percentage Mean Diurnal IOP Reductions During the Treatment Period With Tafluprost Treatment at Different Concentrations in Study P15002

2.2.4.2. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.*

In the Phase 2 dose-finding trials with treatment duration of 4 to 6 weeks, the most common ocular AEs were: conjunctival hyperemia, eye irritation, and eye pruritus. The conjunctival

hyperemia appeared to be dose related: it occurred more frequently in tafluprost 0.005% and 0.0025% than in 0.0015%. The degree of conjunctival hyperemia with 0.0015% tafluprost was similar to that with latanoprost arm.

2.2.4.3. Does this drug prolong the QT or QTc interval? (You must answer this question, unless this is addressed in the question above.)

No, Tafluprost 0.0015% ophthalmic solution following topical ocular administration did not prolong the QT or QTc interval in the clinical trial population. Due to a low systemic exposure to tafluprost and tafluprost acid, a thorough QT study was considered unnecessary and not conducted.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dosing rationale for Phase 3 pivotal trials was based on the dose-response relationship derived from Phase 2 studies (Refer to *Section 2.2.4.1*). An IOP responder analysis provided by the sponsor combining the data from both Phase 2 and 3 trials further supported the selection of the 0.0015% as the appropriate dose strength in tafluprost ophthalmic solution (**Table 2.2.4.4-1**).

Table 2.2.4.4-1: Number (%) of Patients With ≥25% Reduction in Diurnal IOP from Baseline at Week 4/Week 6[†] (Full Analysis Set Population from Phase 2 and 3 Trials; Study Eye)

	Placebo ($N^{‡}$ = 30)		0.0003% ($N^{‡}$ = 28)		0.001% ($N^{‡}$ = 30)		0.0015% ($N^{‡}$ = 948)		0.0025% ($N^{‡}$ = 61)		0.005% ($N^{‡}$ = 30)		Timolol ($N^{‡}$ = 543)		Latanoprost ($N^{‡}$ = 341)	
Number (%) of Patients:	m/n[§]	(%)	m/n[§]	(%)	m/n[§]	(%)	m/n[§]	(%)	m/n[§]	(%)	m/n[§]	(%)	m/n[§]	(%)	m/n[§]	(%)
With ≥25% reduction in diurnal IOP from baseline at Week 4/Week 6	0/30	(0.0)	12/28	(42.9)	11/30	(36.7)	579/938	(61.7)	25/58	(43.1)	10/28	(35.7)	283/537	(52.7)	259/340	(76.2)

[†] Week-4 IOP measurements were used for Studies 15-001, 15-002 and 77550. Week-6 IOP measurements were used for Studies 74457, 74458, 15-003 and 001.

[‡] N = Number of patients in the treatment group.

[§] m/n = Number of patients with ≥25% reduction in diurnal IOP from baseline at Week 4/Week 6 / Number of patients in the analysis.

Missing data were handled using the Last-Observation-Carried-Forward method.

There is no unresolved dosing or administration issues.

2.2.5. What are the PK characteristics of the drug?

2.2.5.1. What are the single dose and multiple dose PK parameters?

Tafluprost PK was studied following 8-day q.d. topical ocular administration of tafluprost 0.0015% preservative-containing (PC) and preservative-free (PF) ophthalmic solution in healthy subjects (Study 77551). The calculated pharmacokinetic parameters are presented in **Table 2.2.5.1-1**. For both formulations, the concentrations of tafluprost acid peaked at a median time of 10 minutes on both Days 1 and 8. Mean plasma concentrations of tafluprost acid were below the limit of quantification (10 pg/mL) at 30 minutes. Pharmacokinetic parameters (AUC and C_{max}) of the PC and PF formulations of tafluprost were comparable (*refer to Section 4.2.2*).

Following 8-day q.d. administration of tafluprost 0.0015% PF ophthalmic solution to healthy subjects, mean plasma tafluprost acid C_{max} were 26 pg/mL and 27 pg/mL on Day 1 and Day 8, respectively; mean plasma tafluprost acid AUC were 394 pg*min/mL and 432 pg*min/mL on Day 1 and 8, respectively, suggesting minimal accumulation. It should be noted that, compared to the PF formulation, C_{max} or AUC differences between Day 1 and Day 8 appears to be more evident for the PC formulation. In fact, the mean tafluprost acid systemic exposure (AUC and

C_{max}) is statistically higher on Day 8 than on Day 1 for the PC formulation. However, the difference is not considered to be clinically relevant due to the low exposure.

Table 2.2.2.5-1: Descriptive statistics for pharmacokinetic parameters of tafluprost acid on Days 1 and 8 (AUC & Cmax: (Mean ± SD); t_{max}: mean (min-max)) following topical ocular administration of tafluprost 0.0015% PF and PC ophthalmic solutions

Day of Treatment Period (n)	$AUC_{0\text{-last}}$(pg*min/ml)	C_{max} (pg/ml)	t_{max} (min) (min – max)
Preserved			
Day 1 (n=16)	405.9±395.2[a]	24.42±15.76[a]	10 (10-15)
Day 8 (n=16)	581.1±529.9[b]	31.43±19.53[b]	10 (5-15)
Unpreserved)			
Day 1 (n=16)	394.3±286.4[a]	26.16±10.35	10 (5-15)
Day 8 (n=16)	431.9±457.8[b]	26.61±18.02[b]	10 (5-15)
[a] Differences between the preserved or unpreserved formulations were not statistically significant on Day 1 (p=0.600 and 0.529 for $AUC_{0\text{-last}}$ and C_{max}, respectively).			
[b] Differences between the preserved or unpreserved formulations were not statistically significant on Day 8 (p=0.462 and 0.294 for $AUC_{0\text{-last}}$ and C_{max}, respectively).			

Table 5 and Table 6 in study report 77551

2.2.5.2. How does the PK of the drug in healthy volunteers compare to that in patients?

Tafluprost PK following topical ocular administration was only evaluated in healthy subjects.

2.2.5.3. What are the characteristics of drug absorption?

Following topical ocular administration, tafluprost is absorbed through the cornea and is hydrolyzed to the biologically active acid metabolite (EC_{50} to the recombinant human FP prostanoid receptor = 217 pg/mL, or 0.5 nM). The plasma concentrations of tafluprost acid peaked at a median time of 10 minutes on both Days 1 and 8.

2.2.5.4. What are the characteristics of drug distribution?

The binding of tafluprost acid to human serum protein (4%) was > 99% (*Study PK017, refer to Section 4.2.3*).

2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination? (This may include table with results of mass balance study.)

A mass balance study was not performed.

2.2.5.6. What are the characteristics of drug metabolism?

Tafluprost, an ester prodrug, is hydrolyzed to its biologically active acid metabolite, tafluprost acid, in the eye. Tafluprost acid is further metabolized via fatty acid β-oxidation and phase II conjugation (*refer to Sections 4.2.4 and 4.2.5)*.

2.2.5.7. What are the characteristics of drug excretion?

No studies were submitted that evaluated the major route(s) of drug excretion in humans.

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

In four Phase 1 dose-escalation studies (74450, 74451, 74452, and 74453), neither tafluprost nor tafluprost acid could be detected when using a bioanalytical method with LLOQ at 0.2 ng/mL (for tafluprost) and 0.1 ng/mL (for tafluprost acid). Tafluprost PK was successfully assessed in two PK studies (P77551 and P15005) following topical ocular administration of tafluprost ophthalmic solution at one dose level (i.e., 0.0015%) when an improved bioanalytical method was used (LLOQ = 10 pg/mL for tafluprost acid). Therefore, the degree of linearity or nonlinearity was not ascertained.

2.2.5.9. How do the PK parameters change with time following chronic dosing?

Refer to *Section 2.2.5.1*.

2.2.5.10. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The systemic exposure to tafluprost following topical ocular administration was only evaluated in healthy subjects. As shown in **Table 2.2.5.1-1**, C_{max} and AUC values of tafluprost acid were variable (CV% >50%). This level of inter-subject variability in systemic exposure is not considered unexpected following topical ocular administration.

2.3. Intrinsic Factors

2.3.1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of the commonly known intrinsic factors including race, gender and age on the PK of tafluprost following topical administration of tafluprost 0.0015% ophthalmic solution has not been studied. Given the low systemic exposure following topical administration, however, dose adjustment is not warranted in patients based on the commonly known intrinsic factors.

2.4. Extrinsic Factors

2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?
Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

The impact of the commonly known extrinsic factors on tafluprost dose-exposure and/or – response has not been evaluated. Because of the systemic exposure is low, the impact, if any, would not be clinically significant. Therefore, no dosage adjustments for extrinsic factors are recommended.

2.4.2. Drug-drug interactions

2.4.2.1. Is there an in vitro basis to suspect in vivo drug-drug interactions?

No. Tafluprost, an ester prodrug, is hydrolyzed to its biologically active acid metabolite, tafluprost acid, in the eye. Tafluprost acid is further metabolized via fatty acid β-oxidation and phase II conjugation. In vitro metabolism studies suggested that tafluprost acid is not metabolized by CYP450 enzymes *(Refer to Section 4.2.6)*.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Neither tafluprost nor tafluprost acid is a substrate of CYP enzymes *(Refer to Section 4.2.6*) nor has metabolism influenced by genetics.

2.4.2.3. Is the drug an inhibitor and/or an inducer of CYP enzymes?

No in vitro inhibition nor in vitro induction studies were performed by the sponsor, thus, it is unknown if tafluprost or tafluprost acid is an inhibitor and/or an inducer of CYP enzymes.

2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No transporter studies were performed by the sponsor, thus, it is unknown if tafluprost or tafluprost acid is an inhibitor and/or substrate of P-glycoprotein transport process.

2.4.2.5. Are there other metabolic/transporter pathways that may be important?

No, there are no other metabolic/transporter pathways expected to be of importance.

2.4.2.6. Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No, the label does not specify co-administration of another drug.

2.4.2.7. What other co-medications are likely to be administered to the target patient population?

Tafluprost 0.0015% ophthalmic solution can be used as adjunctive treatment with timolol. No other co-administered drugs can be specified.

2.4.2.8. Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No in vivo drug-drug interaction studies have been conducted.

2.4.2.9. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for PD drug-drug interactions.

2.4.2.10. Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no unresolved questions related to active metabolites and metabolic drug interactions. However, with respect to the assessment of in vitro metabolism of the active tafluprost acid metabolite, the validity of the experimental condition in the CYP450 reaction phenotyping experiments with the acid metabolite was not confirmed because of the lack of inclusion of positive controls (*Refer to Section 4.2.6*). It should also be noted that plasma protein binding was assessed using constituted human albumin solution instead of pooled human plasma (*Refer to Section 4.2.3*).

2.4.3. What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No issues related to dose, dosing regimens, or administration remain unresolved.

2.5. General Biopharmaceutics

Not applicable. Tafluprost is formulated as an ophthalmic solution for topical ocular administration.

2.6. Analytical Section

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

Tafluprost acid (the active metabolite of tafluprost) plasma concentrations were quantified using an adequately validated liquid chromatography (LC) assay with tandem mass spectrometric detection (MS/MS). Tafluprost acid and the internal standard, (b) (4), were extracted from human plasma by liquid-liquid extraction.

2.6.2. Which metabolites have been selected for analysis and why?

Tafluprost acid was selected for analysis because it is the primary and pharmacologically active metabolite of tafluprost.

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

Total tafluprost acid concentrations in the plasma were measured. Free concentrations in the plasma are not considered clinically relevant following ocular topical administration.

2.6.4. What bioanalytical methods are used to assess concentrations?

Refer to Section 2.6.1. for further information.

2.6.4.1. 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 standard curve in plasma ranged from 10 pg/mL to 5000 pg/mL for tafluprost acid. The ranges of standard curve are adequate for purposes of determining plasma concentrations of tafluprost acid in the clinical studies.

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

The LLOQ and ULOQ are 10 pg/mL and 5000 pg/mL in the undiluted plasma sample, respectively.

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

The assay accuracy and precision were determined from the assay standards and QCs. The accuracy values ranged from 87.8% to 105.8%. The precision values ranged from 0% to 10.3%. Assay selectivity was confirmed by analyzing six naïve human plasma samples and none yielded above BLQ results.

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

Tafluprost acid was stable in stock solution stored at room temperature up to 6 hours and at -10°C to -30°C for 32 days, following six freeze/thaw cycles, in processed sample stored in the autosampler (15 °C) for 23 hours and at 2°C to 8°C for 126 hours, and in frozen matrix stored at -10°C to -30°C for 28 days.

2.6.4.5. What is the QC sample plan?

Four QCs prepared in plasma at a concentration of 30, 800, 1500 (diluted QC), and 3500 pg/mL of tafluprost acid. Between-run and within-run accuracy and precision were evaluated using replicates (n=6) from each of these concentrations were included in each analysis.

3. LABELING RECOMMENDATIONS

See Appendix 4.1. for detail.

4. APPENDICES

4.1. Proposed Package Insert (Original and Annotated) with Clinical Pharmacology edits (noted as underline and strikethrough) as of 15July2011

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2. Individual Study Reviews

4.2.1. Pharmacokinetics of tafluprost in healthy subjects: Study P15005

Study Number: P15005
An Open-Label, Single-Center Study Evaluating the Pharmacokinetics, Safety, and Tolerability of Tafluprost 0.0015 % Ophthalmic Solution in Healthy Subjects (Phase 1)

Dates: 26 May, 2005 to 11 June, 2005
Study Director: (b) (4)
Analytical site: (b) (4)

OBJECTIVES:

The objective was to investigate the pharmacokinetics, safety and tolerability of tafluprost 0.0015% ophthalmic solution after single and repeated dosing in healthy adult subjects.

FORMULATION & ADMINISTRATION

Tafluprost 0.0015 % (batch no. C000401) eye drops; One drop in each eye at approximately 8:00 a.m. each day for 8 days.

STUDY DESIGN:

This was a non-randomized, open-label and single-center Phase 1 study evaluating the pharmacokinetics, safety, and tolerability of tafluprost 0.0015 % ophthalmic solution in healthy subjects (n=19).

Following screening visit, eligible subjects were treated with tafluprost 0.0015 % ophthalmic solution for a period of 8 days. Subjects were dosed once in each eye in the mornings. Subjects received their first and last tafluprost dose in the clinic (at Day 1 and Day 8), and dosed at home on Days 2 to 7.

Blood samples for pharmacokinetic analysis were obtained on Days 1 and 8 at the following time points: pre-dose, post-dose at 5, 10, 15, 30, 45 minutes, and 1, 2, and 4 hours.

Subjects were queried regarding AEs, and evaluations were performed for corrected visual acuity, ocular symptoms, biomicroscopy, conjunctival redness, ophthalmoscopy, and intraocular pressure (IOP). Subjects were also queried regarding overall drop discomfort.

Demographic characteristics are summarized in **Table 1**.

Table 1: Demographic Characteristics

Subject number	Subject Initials	Visit date	Date of Birth	Age	Race	Race, specify	Iris color	Iris color, specify
04501	(b) (6)	05/31/05	(b) (6)	35	White		Blue	
04502		06/01/05		22	Black or African American		Brown	
04503		06/01/05		26	Hispanic		Other	HAZEL
04504		06/02/05		31	Hispanic		Brown	
04505		05/26/05		23	Hispanic		Brown	
04506		05/27/05		27	White		Blue	
04507		05/31/05		29	White		Brown	
04508		05/27/05		23	Hispanic		Brown	
04509		06/01/05		22	Hispanic		Brown	
04510		05/31/05		19	White		Other	HAZEL
04511		05/31/05		19	White		Blue	
04512		06/03/05		26	Hispanic		Brown	
04513		06/02/05		31	Hispanic		Brown	
04514		05/27/05		24	Hispanic		Brown	
04515		06/01/05		24	White		Other	HAZEL
04516		05/27/05		27	Hispanic		Brown	
04517		06/03/05		19	Black or African American		Brown	
04518		05/26/05		30	Other	INDIAN/ASIAN	Brown	
04519		05/27/05		38	Black or African American		Other	HAZEL

ASSAY METHODOLOGY:

Tafluprost acid (AFP-172, the active metabolite of tafluprost) plasma concentrations were quantified using an adequately validated liquid chromatography (LC) assay with tandem mass spectrometric detection (MS/MS). AFP-172 and the internal standard (IS), (b) (4), were extracted from human plasma by liquid-liquid extraction. For the mass spectral detection, the following precursor product ions were monitored: 409.1→213.1 for AFP-172 and 443.0→213.1 for IS.

This assay was calibrated using a standard curve generated from eight non-zero AFP-172 standards (10, 20, 100, 400, 1000, 2000, 4000 and 5000 pg/mL). In addition, QCs prepared in plasma at concentrations of 30, 800, 3500 pg/mL, and 1500 (diluted QC) pg/mL of AFP-172 were included in each analysis.

Criterion	Tafluprost acid (AFP-172)	Comments
Conc. range, pg/mL	10-5000 (0.500 mL sample)	satisfactory
LLOQ, pg/mL	10	satisfactory
Linearity, r^2	1.00	satisfactory
Accuracy, % RE	-3.5% – 5.8% [a] 0.0% – -4.3% [b] -12.2% – 0.7% [c]	Satisfactory
Precision, % CV	0.0% – 8.2% [a] 4.4% – 5.4% [b] 1.4% – 10.3% [c]	Satisfactory
Selectivity	Six lots of human plasma samples yielded BLQ results	Satisfactory
Recovery	QC samples: 85.4 – 85.7%	Satisfactory
Stability	Stable when stock solution stored at room temperature up to 6 hours and at -10°C to -30°C for 32 days, following six freeze/thaw cycles; when processed sample stored in the autosampler (15 °C) for 23 hours and at 2°C to 8°C for 126 hours, when frozen matrix stored at -10°C to -30°C for 28 days.	satisfactory

[a], Inter-assay for standards; [b], Inter-assay for QCs; [c], Intra-assay for QCs
From Report 0170 (b) (4) study # 6776-110)

DATA ANALYSIS

Descriptive statistics for AFP-172 (the active metabolite of tafluprost, i.e. AFP-168) pharmacokinetic parameters including plasma C_{max}, $AUC_{0\text{-last}}$, and t_{max} was determined, as well as Student's paired t-test (Day 1 vs. Day 8) for $AUC_{0\text{-last}}$ and C_{max}.

Safety and tolerability assessments: Adverse events, visual acuity, conjunctival redness, biomicroscopy, ocular symptoms, ophthalmoscopy, intraocular pressure (IOP) and overall drop discomfort.

RESULTS:

Pharmacokinetics

The individual and mean concentration-time profiles of AFP-172 on Days 1 and 8 are shown in **Figures 1** and **2**, respectively. On both days, mean concentrations peaked at 10 minutes and decreased rapidly thereafter. After 30 min post-dose, all the samples were below the LLOQ of 10 pg/mL.

The mean concentrations were consistently higher at Day 8. However, for five out 19 subjects, $AUC_{0\text{-last}}$ and C_{max} were actually lower on Day 8 (**Figure 3**).

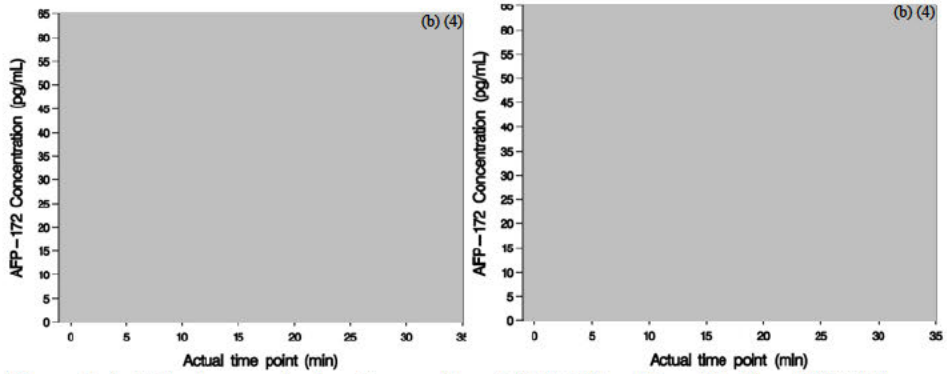
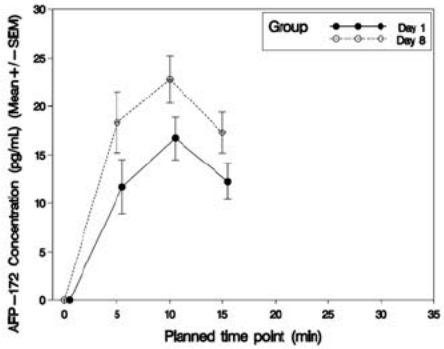


Figure 1: Individual concentration-time profiles of AFP-172 on Days 1(left) and 8 (right).



Source: Clinical study report 15005

Figure 2: Mean Concentration-time profile of AFP-172 on Days 1 and 8.

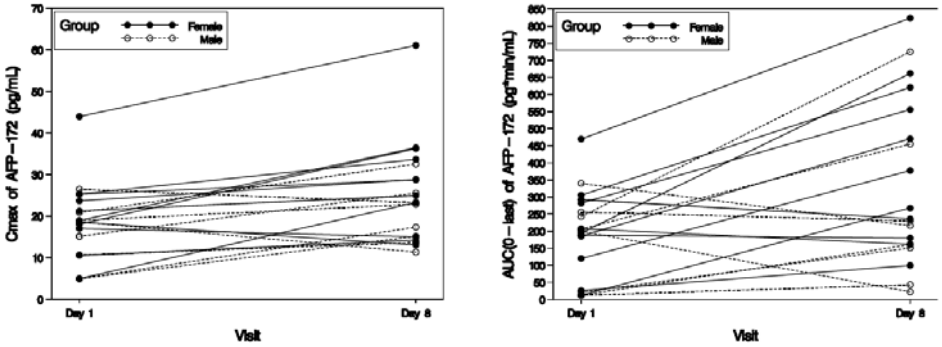


Figure 3: Individual C_{max} and $AUC_{0\text{-last}}$ values of AFP-172 on Days 1(left) and 8 (right).

Summary statistics for pharmacokinetic parameters are presented in **Table 1**. A slight increase in $AUC_{0\text{-last}}$ (1.8-fold higher) and C_{max} (1.4-fold higher) was seen from Day 1 to Day 8.

Table 1: Descriptive statistics for Pharmacokinetic Parameters of AFP-172 on Days 1 and 8

	$AUC_{0\text{-last}}$ (pg*min/mL)	C_{max} (pg/mL)	t_{max} (min)
Day 1 (N=19)	188.3 ± 128.1[a]	18.37 ± 9.23[b]	10 (5-16)[c]
Day 8 (N=19)	340.2 ± 242.4	25.17 ± 11.92	10 (5-15)

Statistically significant differences between day 1 and day 8: [a] p = 0.013, [b] p = 0.007; [c] N=16

SAFETY RESULTS:

All 19 subjects completed the study. Nine subjects out of 19 reported a total of 22 adverse events. The majority of the adverse events were ocular, and most of the events were mild. The most prevalent adverse event was (mostly mild) ocular redness, reported by 7 out of 19 subjects. There were neither serious adverse events nor premature discontinuations due to adverse events in this study.

The mean IOP was reduced by approximately 3 mmHg from screening to Day 8.

SPONSORS CONCLUSIONS:

Mean AFP-172 plasma concentrations increased slightly from Day 1 (single dosing) to Day 8 (repeated dosing). AFP-172 plasma concentrations were low at all time points with the highest mean concentrations of 16.7 pg/mL (Day 1) and 22.8 pg/mL (Day 8). These values are about 2-fold of the lower limit of quantification (i.e., 10 pg/mL).

Both on Day 1 and Day 8, the pre-dose concentrations of AFP-172 were below the lower limit of quantification in all subjects. Furthermore, AFP-172 plasma concentrations were below the LLOQ in all of the subjects beyond 30 minutes after instillation. The mechanism(s) behind the slightly elevated concentrations of AFP-172 in plasma after repeated ocular administration of tafluprost cannot be definitely concluded from the present data.

Nine subjects out of 19 reported adverse events. Most of the adverse events were ocular and mild in severity. Ocular redness was reported in 7 subjects, which is common for this class of drugs. No unexpected findings were detected in the ocular safety variables and overall drop discomfort. In summary, tafluprost was well tolerated and safe.

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Results from Study 15005 adequately assessed the pharmacokinetics of tafluprost following repeated topical ocular administrations of tafluprost 0.0015 % preservative containing eye drops. The sponsor's conclusions are valid. The reviewer has additional comments as follows:

- Although the mean AFP-172 concentrations increased 1.8-fold from Day 1 to Day 8, there are a few subjects (5 out of 19) who had lower AFP-172 $AUC_{0\text{-last}}$ and C_{max} values on Day 8 than on Day 1. Given the low systemic exposure, the potential small difference in mean AFP-172 plasma concentrations is not likely to have clinical significance.

4.2.2. PK of tafluprost: preservative-containing vs. preservative-free eye drop (Study P77551)

Study Number: P77551
Pharmacokinetics of tafluprost 0.0015 % eye drops: a comparison between the preserved and unpreserved formulation in healthy subjects (Phase 1)

Dates: 20 September 2005 to 22 December 2005
Study Director: (b) (4)
Analytical Site: (b) (4)

OBJECTIVES:

The objective of the study was to investigate the pharmacokinetics of the preserved and unpreserved formulation of tafluprost 0.0015 % eye drops in healthy subjects

FORMULATION & ADMINISTRATION

Tafluprost 0.0015% preserved (batch No. C000401) and tafluprost 0.0015% unpreserved (batch No.102844) eye drops, one drop in each eye at 20:00 daily for 8 days (preserved or unpreserved drops) plus 8 days (unpreserved or preserved drops) in a cross-over design.

Tafluprost 0.0015 % preserved formulation eye drops were formulated as follows and were available in bottles:

- Tafluprost 0.015 mg
- Polysorbate 80 q.s.
- Sodium dihydrogen phosphate dihydrate q.s.
- Disodium edetate q.s.
- Glycerol q.s.
- Benzalkonium chloride (b) (4)
- Dilute Sodium hydroxide and /or
- Dilute Hydrochloride acid, concentrated q.s.
- Water for injections (b) (4)

Tafluprost 0.0015 % unpreserved formulation eye drops were formulated as follows and were available in single use containers:

- Tafluprost 0.015 mg
- Polysorbate 80 q.s.
- Sodium dihydrogen phosphate dihydrate q.s.
- Disodium edetate q.s.
- Glycerol q.s.
- Dilute Sodium hydroxide and /or
- Dilute Hydrochloride acid, concentrated q.s.
- Water for injections (b) (4)

STUDY DESIGN:

This is a Phase 1, single center, investigator-masked, randomized, two-period cross-over PK study. Duration of treatment is 16 days (8 days for each formulation) with a wash-out of at least 4 weeks between treatments. N=16 healthy subjects, 8 per treatment sequence.

Blood samples for pharmacokinetic analysis were obtained on Days 1 and 8 at the following time points: pre-dose, post-dose at 5, 10, 15, 30, 45 minutes, and 1, 2, and 4 hours.

Demographic characteristics are summarized in **Table 1**.

Table 1: Demographic characteristics

Variable	N	MEAN	SD	SE	MIN	MEDIAN	MAX
Age	16	29.2	7.8	2.0	18	29	43

Variable		N	%
Sex	Male	7	43.8
	Female	9	56.3
Race	Caucasian	16	100.0
Iris color	Blue/Gray	3	18.8
	Blue/Gray -brown	2	12.5
	Green	1	6.3
	Green -brown	4	25.0
	Brown	3	18.8
	Other	3	18.8
Female of childbearing potential	Yes	9	100.0
Chemical contraception	Yes	6	.
IUD	Yes	2	.
Other	Yes	2	.
Pregnancy test result	Negative	9	100.0

ASSAY METHODOLOGY:

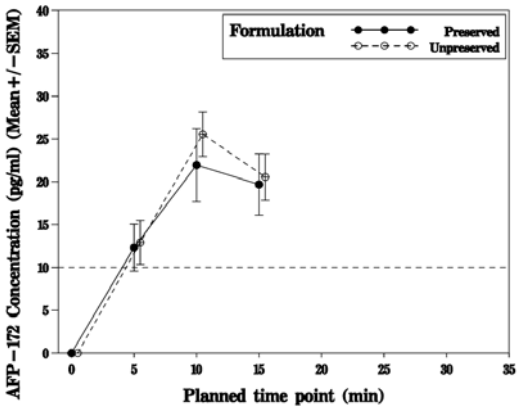
Quantitation of AFP-172 in human plasma was reviewed and described in *Section 4.2.1.* (Study P15005). QC samples were included in the study and results were considered satisfactory.

DATA ANALYSIS

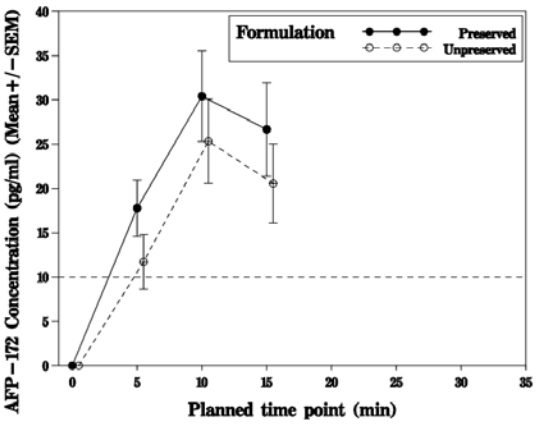
A repeated measurement analysis of variance was used for evaluation of the AFP-172 and nonparametric analysis of variance model for $AUC_{0\text{-last}}$ and C_{max}. Descriptive statistics for t_{max} and safety variables were used.

RESULTS:

Pharmacokinetics
Figures 1 & **2** summarize the mean (± SEM) concentrations of AFP-172 at Days 1 and 8, respectively. Individual $AUC_{0\text{-last}}$ and C_{max} values by formulation are presented in **Figures 3** & **4**. The intrasubject variation was large for both parameters. No trends were detected between the two formulations.



Source: Clinical study report P77551
Figure 1: Mean Concentration-time profile of AFP-172 on Day 1: Preserved vs. unpreserved



Source: Clinical study report P77551
Figure 2: Mean Concentration-time profile of AFP-172 on Day 8: Preserved vs. unpreserved

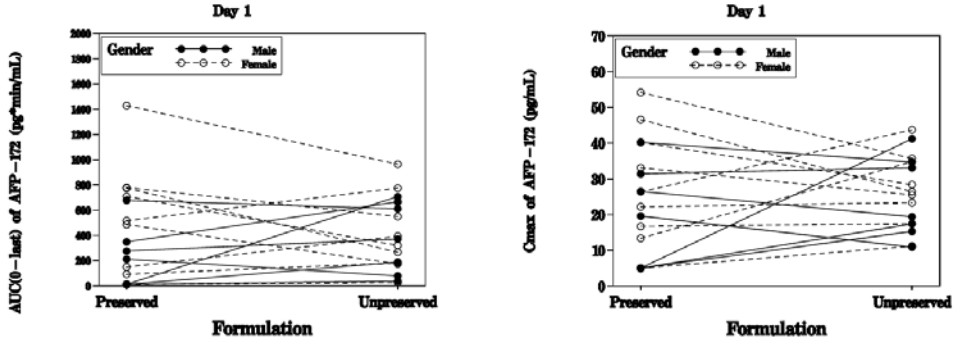


Figure 3: Individual C_{max} and $AUC_{0\text{-last}}$ values of AFP-172 by formulation on Day1

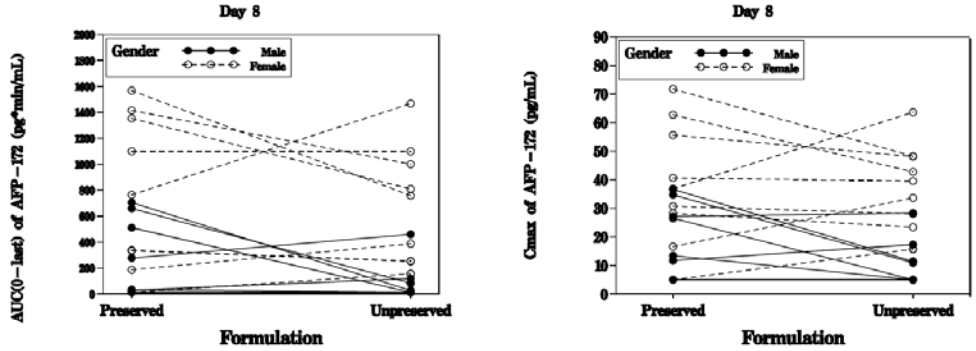


Figure 4: Individual C_{max} and $AUC_{0\text{-last}}$ values of AFP-172 by formulation on Day8.

Summary statistics for the pharmacokinetic parameters are presented in **Tables 2** and **3**. $AUC_{0\text{-last}}$ (p=0.600 and 0.462) and C_{max} (p=0.529 and 0.294) values were comparable between the preserved and unpreserved formulation on Days 1 and 8, respectively. For both formulations, the concentrations of AFP-172 peaked at a median time of 10 minutes on both Days 1 and 8.

Table 2: Descriptive statistics for pharmacokinetic parameters (mean ± SD for $AUC_{0\text{-last}}$ and C_{max}; median and range for t_{max}) on Day 1

	$AUC_{0\text{-last}}$ (pg*min/mL)	C_{max} (pg/mL)	t_{max} (min)
Preserved (N=16)	405.9 ± 395.2[a]	24.41 ± 15.76[b]	10 (10-15)[c]
Unpreserved (N=16)	394.3 ± 286.4	26.16 ± 10.35	10 (5-15)

Non-parametric ANOVA (preserved vs. unpreserved formulation): [a] p=0.600, [b] p =0.529; [c] N=12

Table 3: Descriptive statistics for pharmacokinetic parameters (mean ± SD for $AUC_{0\text{-last}}$ and C_{max}; median and range for t_{max}) on Day 8

	$AUC_{0\text{-last}}$ pg*min/mL	C_{max}, pg/mL	T_{max}, min
Preserved (N=16)	581.1± 529.9 [a]	31.43±19.53 [b]	10(5-15)
Unpreserved (N=16)	431.9±457.8	26.61±18.02	10(5-15)

Non-parametirc ANOVA (preserved vs. unpreserved formulation): [a], p=0.462; [b], p=0.294.

Intraocular Pressure:
The IOP was evaluated at Screening, Day 1 (before dosing and 4 hours after dosing), Day 8 (before dosing and 4 hours after dosing) and Post-study. The results are presented in **Figure 5**. The IOP lowering effect of the two formulations was comparable over the course of the study. The decrease in the mean IOP (of the two treated eyes) e.g. from Day 1 (before dosing) to Day 8 (4 hours after dosing) was -3.50 mmHg for the preserved formulation and -3.64 mmHg for the unpreserved formulation.

Reviewer's comments: *This comparison is based on the limited number of IOP measurement and IOP reduction data from healthy subjects. Therefore, the conclusion regarding the similar IOP reduction effect observed for both formulations can not be necessarily extrapolated to the patient population.*

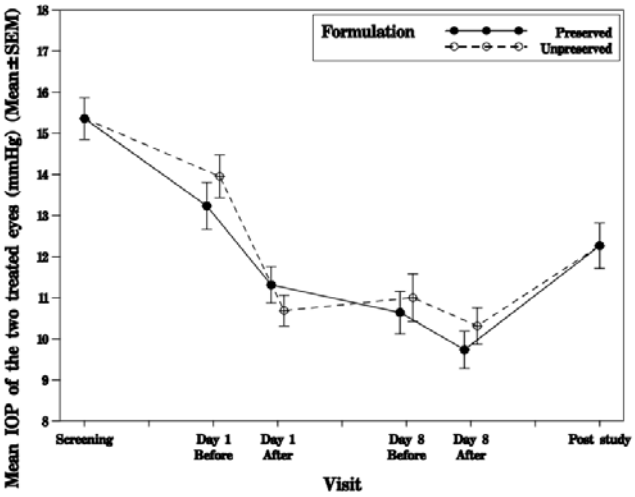


Figure 5: Mean IOP (of the two treated eyes) during the study

SAFETY RESULTS:

A total of 36 adverse events were reported by 16 subjects for the preserved formulation, whereas a total of 27 adverse events were reported by 16 subjects for the unpreserved formulation. A majority of the adverse events were ocular. All adverse events were mild or moderate in severity, except one severe ocular hyperemia for the preserved formulation. The most common ocular adverse event was ocular hyperemia reported in 16 subjects for the preserved formulation and in 15 subjects for unpreserved formulation. The severity of ocular hyperemia was, however, mostly moderate for the preserved formulation and mostly mild for the unpreserved formulation. Conjunctival redness (in biomicroscopic examination) was also slightly more prominent for the preserved formulation on Day 8.

SPONSORS CONCLUSIONS:

The systemic exposure was comparable between the preserved and unpreserved formulations on both days. The plasma concentrations of AFP-172 (the active metabolite of tafluprost) had a similar profile and were low at all time points following single (Day 1) and repeated (Day 8) topical administration of 0.0015 % preserved and unpreserved tafluprost eye drops. The mean AFP-172 concentrations, C_{max} values (24.4 and 31.4 pg/mL) and $AUC_{0\text{-}last}$ values (405.9 and 581.1 pg*min/mL) of the preserved formulation were slightly higher on Day 8 than on Day 1. The mean AFP-172 concentrations, C_{max} values (26.2 and 26.6 pg/mL) and $AUC_{0\text{-}last}$ values (394.3 and 431.9 pg*min/mL) of the unpreserved formulation were similar on Days 1 and 8. However, the differences were small and statistically insignificant between the unpreserved and preserved formulation on both days (e.g. 4.8 pg/mL in C_{max} on Day 8, which is below the lower limit of quantification, 10 pg/mL).

All 16 subjects reported adverse events for both formulations. A majority of the adverse events were ocular and mild or moderate in severity. Ocular hyperemia was reported by 15 subjects for the unpreserved formulation and by 16 subjects for the preserved formulation, which is common for this class of drugs. There were neither serious adverse events nor premature discontinuations

due to adverse events in this study. No unexpected findings were detected in the ocular safety variables or systemic safety variables. Both formulations were well tolerated and safe.

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Results from Study P77551 adequately compared the pharmacokinetics of tafluprost following repeated ocular instillation of preservative-containing vs. preservative-free tafluprost 0.0015% eye drops. The sponsor's conclusions are valid.

4.2.3. Evaluation of AFP-172 binding to human serum albumin by ultrafiltration method

Study Number: PK017
Dates: 09 July, 2002 to 26 July24, 2002
Title: Evaluation of the binding ratios of AFP-172 to Rat, Rabbit, Dog and Human Serum Albumin by Ultrafiltration Method

Objectives:
To assess the *in vitro* serum protein binding of AFP-172 in human and various animal species.

Study Design:
Serum albumin (0.8 and 1.2 g) of each species was added into 20 and 30 mL of 0.0667 mol/L phosphate buffer, respectively, and dissolved (4% serum albumin solution; *Note: the normal range of plasma albumin concentration is 3.5% to 5.2%*).

AFP-172 solution (15 µL) was added to 1.5 mL of serum albumin solution in a glass tube as listed in the table below and well mixed (n = 3 at each concentration / each species). (b) (4)

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Final AFP-172 concentration (ng/mL)	AFP-172 solution concentration (ng/mL)	Volume of AFP-172 solution (µL)	Number of samples
1*	100	15	3
10	1000	15	3
100	10000	15	3
500	50000	15	3

* The samples of 1 ng/mL of AFP-172 in serum albumin solution were prepared for only rabbit and human serum albumin.

The binding ratio (*BR*) of AFP-172 determined by ultrafiltration was calculated from the expression:

$$BR\% = \frac{C_p - C_f}{C_p} \times 100$$

where C_p is the nominal concentration of AFP-172 in serum albumin solution, and
C_f is the mean measured concentration of AFP-172 in the filtrate

Analytical Methods:
The concentration of AFP-172 was measured by a LC-MS/MS method. In the study report submitted, the assay accuracy (human) was provided for both calibration standards and QC samples:

Batch No.	Species	Back-calculated concentrations (ng/mL)								Slope	Intercept	r
		STD 1 0.4 ng/mL	STD 2 1 ng/mL	STD 3 5 ng/mL	STD 4 10 ng/mL	STD 5 50 ng/mL	STD 6 90 ng/mL	STD 7 120 ng/mL	STD 8 150 ng/mL			
Batch020710 (Accuracy %)	Human	(b) (4)										

Batch No.	Measured concentrations (ng/mL)					
	LLOQ-1	LLOQ-2	MeQC-1	MeQC-2	ULOQ-1	ULOQ-2
	0.4 ng/mL	0.4 ng/mL	10 ng/mL	10 ng/mL	150 ng/mL	150 ng/mL
Batch020710 (Accuracy%)	(b) (4)					

Reviewer's comments: *Except for the assay accuracy assessment provided by the sponsor, the other important parameters for a bioanalytical method validation including precision, recovery and stability were not provided in the study report. In addition, no control study using known low-, medium-, or high-protein bound substrate appears to have been performed in the study to validate the experimental conditions.*

Sponsor's Results:

The binding ratios of AFP-172 to rat, rabbit and dog serum albumin were in the range of 92.6%-97.0% at the levels of 10-500 ng/mL AFP-172 in serum albumin solutions. The binding ratio to human serum albumin was 99.2% at 500 ng/mL of AFP-172 in serum albumin solutions (**Table 1**). The binding at 1-100 ng/mL AFP-172 in human serum albumin solutions were not obtained because the concentrations of AFP-172 in the filtrate could not be determined by LC-MS/MS.

Table 1: Protein binding of AFP-171 to Human Serum Albumin

	Concentrations (ng/mL)			
	Nominal concentrations (ng/mL)			
	1	10	100	500
Rep. 1	BLOQ	BLOQ	(b) (4)	(b) (4)
Rep. 2	BLOQ	BLOQ	BLOQ	
Rep. 3	BLOQ	BLOQ	BLOQ	
Mean	NC	NC	NC	4.059
Binding %	NC	NC	NC	99.2

Rep.: replicate
BLOQ: below lower limit of quantitation (0.4 ng/mL)
NC: not calculable

Reviewer's assessment and Recommendations:

Study PK017 assessed human plasma protein binding of AFP-172 by using the constituted human serum albumin solution. The study is not considered acceptable in characterizing plasma protein binding of AFP-172 from a clinical pharmacology perspective, due to the following considerations:

- Although the major plasma protein to bind the acidic AFP-172 (i.e., the active carboxylic acid metabolite of tafluprost) is likely to be the basic albumin, there are other plasma proteins that can potentially bind AFP-172 in the plasma. A preferred method to assess the plasma protein binding of AFP-172 is using pooled human plasma instead of the constituted human albumin solution.
- The full validation report for the LC-MS/MS method used in the study was not provided, therefore, the validity of the study could not be fully assessed.

In conclusion, the sponsor's assessment of AFP-172 plasma protein binding will not be used to support any regulatory decisions regarding AFP-172 distribution characteristics in human.

4.2.4. In Vitro Metabolism Study on Tafluprost and AFP-172 Using Cryopreserved Hepatocytes

Study Number: PK023
Dates: 20 October 2005 to 21 March 2006
Study Location: (b) (4)

Title: In Vitro Metabolism of [^{3}H]-AFP-168 and AFP-172 by Rat, Monkey, and Human Hepatocytes ((b) (4) Report # 7016-124)

Objectives:
To determine the rates of metabolism and metabolic profile of [^{3}H]-AFP-168(Tafluprost) and AFP-172(Tafluprost acid) in vitro using rat, monkey, and human hepatocytes.

***Reviewer's Comment**: This review is only focused on the results using human hepatocytes.*

Study Design:
The metabolism of [^{3}H]-AFP-168 and AFP-172 was examined in isolated hepatocytes from Sprague-Dawley (SD) rats, Cynomolgus monkeys, and humans. Hepatocytes were suspended in William's E medium and incubated with either [^{3}H]-AFP-168 or AFP-172 at a final concentration of 100 µM at 37°C in an atmosphere of 5% CO_2 for 0, 120, and 240 minutes. Hepatocyte incubations were terminated by addition of ACN and analyzed for AFP-168, AFP-172 and metabolites by liquid chromatography/mass spectrometry (LC/MS).

Metabolic activity of the hepatocytes for the study was validated by measuring integrated Phase I (7-ethoxycoumarin O-deethylase) and Phase II (sulfation and glucuronidation) activities. Primary hepatocytes (approximately1 x 10^6 hepatocytes/mL in William's E medium) were incubated at 37°C in an atmosphere of 5% CO_2. Metabolic activity was assessed by the addition of 10 µL of 10 mM 7-ethoxycoumarin (positive control) to hepatocytes after 0, 120, and 240 minutes of incubation. Thirty minutes after the addition of 7-ethoxycoumarin at the appropriate time point, incubations were terminated with 2.0 mL of acetonitrile (ACN). Samples were (b) (4) for 10 minutes at 4°C. 7-Hydroxycoumarin and conjugated metabolites in the supernatant were quantitated by liquid chromatography/tandem mass spectrometry (LC/MS/MS).

Analytical Methods:
Samples from the hepatocyte incubations were analyzed for [^{3}H]-AFP-168, AFP-172, and other metabolites by LC/MS. Analysis was conducted using Multiple Reaction Monitoring (MRM)/Information Dependent Acquisition (IDA)/Enhance Product Ion (EPI) to determine the metabolite composition in each species.

Results*:*

Positive control
The metabolic activity of the hepatocytes was evaluated and confirmed by 7-ethoxycoumarin O-deethylation (ECOD, Phase I metabolism) and conjugation with glucuronic acid or sulfate (Phase II metabolism).

AFP-168 (Tafluprost)
[^{3}H]-AFP-168 was completely metabolized to various metabolites following incubation with human hepatocytes for 240 minutes. In human samples for LC/MS analysis, eleven metabolites

were putatively identified: AFP-172; 1, 2-dinor-AFP-172; 1, 2, 3, 4-tetranor-AFP-172; hydroxy-1, 2-dinor-AFP-172; hydroxy-1, 2, 3, 4-tetranor-AFP-172; and six (numbered 1 to 6) glucuronides of AFP-172.

AFP-172
Following incubation of AFP-172 with human hepatocytes for 240 minutes, AFP-172 and ten different metabolites were observed: 1,2-dinor-AFP-172; 1,2,3,4-tetranor-AFP-172; hydroxy-1,2-dinor-AFP-172; hydroxy-1,2,3,4-tetranor-AFP-172; and six (numbered 1 to 6) glucuronides of AFP-172.

Sponsor's Conclusions:

Following the incubation of either [^{3}H]-AFP-168 or AFP-172 with cryopreserved human hepatocytes, the following metabolites, 1, 2-dinor-AFP-172, 1, 2, 3, 4-tetranor AFP-172, hydroxy-1, 2-dinor-AFP-172, hydroxy-1, 2, 3, 4-tetranor-AFP-172 and AFP-172 were detected in all samples analyzed. A total of six potential glucuronides of AFP-172 were detected.

Reviewer's assessment and Recommendations:

The study PK023 assessed the metabolite fate of either [^{3}H]-AFP-168 or AFP-172 when incubated with cryopreserved human hepatocytes. The study suggested that under the tested conditions, AFP-168 (Tafluprost) converts to AFP-172 (Tafluprost acid), which is further metabolized into other metabolites including six glucuronide conjugates.

The study is acceptable from a clinical pharmacology perspective. The sponsor's conclusions are valid.

4.2.5. Metabolite Profiling and Identification for Tafluprost

Study Number: PK028
Dates: 16 April 2004 to 12 November 2004
Study Location: (b) (4)

Title: CHARACTERISATION OF PHASE I AND PHASE II METABOLITES IN BIOLOGICAL SAMPLES FROM RAT AND CYNOMOLGUS MONKEY IN VIVO STUDIES AND HUMAN IN VITRO STUDIES FOR [^{3}H]-AFP-168

Objectives:
The purpose of this study was two-fold, firstly to determine the chemical identity of the principal Phase I and Phase II metabolites of AFP-168 found in rat and cynomolgus monkey (i.e., the species used for safety testing of the drug) in vivo, and therefore determine its biotransformation pathways.

The second objective of the study was to determine the chemical identities of the principal Phase I and Phase II metabolites of AFP-168 found in human microsomes, including two human specific metabolites (HMF-2 and HMF-5) found during comparative in vitro metabolism studies.

***Reviewer's Comment**: This review is only focused on the results using human biological matrix.*

Study Design:

Human Microsome
Human liver microsomes used in this study were from a stock (assigned (b) (4) batch no. HHM18.12.03, based on the date of receipt) that was prepared and pooled from 15 human donors supplied by (b) (4).
Upon receipt, the pooled microsomes were thawed into a flask, mixed, divided into aliquots of smaller volume and stored at -75°C. Microsomes were characterized in terms of protein and cytochrome P450 concentrations prior to use.

All reaction mixtures contained potassium phosphate buffer, microsomal protein (2 mg/mL), NADPH (2 mM) and UDPGA (16 mM) in a total volume of 0.5 mL. (b) (4)

(b) (4)
analysis by a HPLC method.

Human Hepatocytes

Human cryopreserved hepatocytes (batch M00995, lots 122, CPN, LAE and IEM) were supplied by (b) (4). All cryopreserved hepatocytes were delivered frozen (b) (4) and were immediately transferred to (b) (4) storage where they remained until required. Before use, the hepatocytes from different lots were thawed and pooled together. Hepatocytes were characterized in terms of cell viability, protein concentration and ability to metabolize 7-ethoxy [3-^{14}C] coumarin prior to use.

Incubation components were mixed together in the following order: (b) (4)

(b) (4)

(b) (4)

(b) (4)

The sample was then transferred to a HPLC vial for direct injection into the liquid chromatograph.

(b) (4)

Analytical Methods:
A mixed standards solution containing AFP-168, AFP-172, 1,2-dinor-AFP-172, 1,2,3,4- tetranor-AFP-172, 1,2,3,4-tetranor-AFP-172 lactone, and the glucuronic acid conjugates of 1,2-dinor-AFP-172 and 1,2,3,4-tetranor-AFP-172was analyzed by HPLC. LC-MS and LC-MS/MS analysis of the concentrated in vitro sample following incubation of ^{3}H-AFP-172 with human microsome and hepatocytes was carried out using negative ion electrospray ionization.

Results:
Positive control

The metabolic viabilities of the hepatocytes used in the preliminary and main in vitro incubations were assessed and confirmed by incubating 7-ethoxy [3-^{14}C] coumarin (50 μM) in parallel to the 3H-AFP-168 incubations.

Human microsome and hepatocyte
In vitro experiments using human liver microsomes showed that in the absence of UDPGA, the pro-drug substrate (AFP-168) was essentially 100% converted to the active drug (AFP-172) and in the presence of UDPGA, the AFP-172 readily undergoes glucuronidation.

The proposed biotransformation pathway in vitro (human) for AFP-168, based on data obtained during this study, is shown in **Figure 1**.

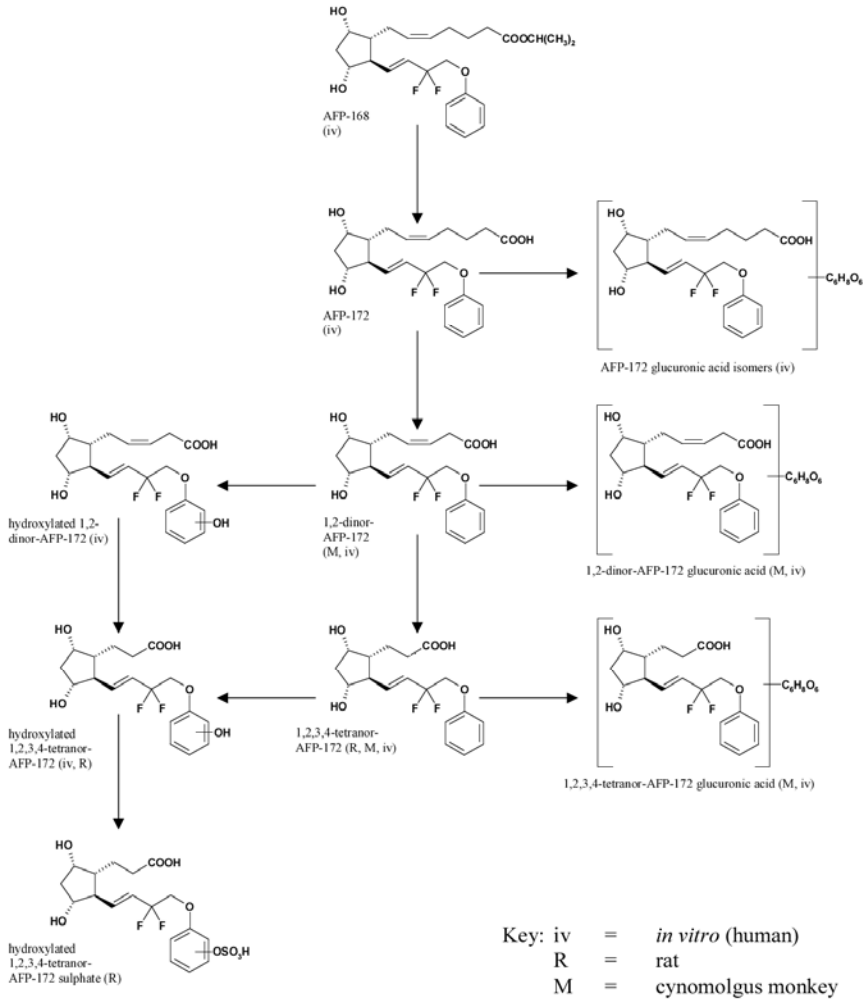


Figure 1: Proposed biotransformation pathway in vivo (rat and monkey) and in vitro (human) of AFP-168. Metabolites were identified via LC/MS

Sponsor's Conclusions:

Incubation of ^{3}H-AFP-168 (100 μM) with human hepatocytes indicated that the acid AFP-172 and its β-oxidized 1, 2-dinor analogue were the main biotransformation products. Further metabolites also identified by mass spectrometry were 1, 2, 3, 4-tetranor-AFP-172 and phenyl ring hydroxylated derivatives of both of these α-side chain shortened acids. Glucuronic acid conjugates of AFP-172, dinor-AFP-172 and tetranor-AFP-172 were also observed in vitro.

Reviewer's assessment and Recommendations:

The in vitro part of the study PK028 was designed to characterize the metabolic profile of [^{3}H]-AFP-168 following incubation with human microsome and cryopreserved human hepatocytes. The data suggests that tafluprost is hydrolyzed to its biologically active metabolite AFP-172, which is further metabolized likely via fatty acid β-oxidation and phase 2 conjugation. Such β-oxidation degradations of the α-side chain are well documented metabolic pathways for related prostaglandins such as 15-deoxy PGF2α and latanoprost, as they are for long chain fatty acids in general.

The study is acceptable from a clinical pharmacology perspective. The sponsor's conclusions are valid.

4.2.6. Reaction Phenotyping for Tafluprost Acid Metabolism Using Human Recombinant CYP450s

Study Number: PK032
Dates: 14 September 2005 to 26 December 2006
Study Location: Santen Pharmaceutical Co., Ltd, Japan.
Title: In vitro reaction phenotyping study of AFP-172 with human recombinant CYP450s

Objectives:
To conduct reaction phenotyping of AFP-172, des-isopropyl metabolite of tafluprost, with 12 human recombinant CYPs.

Methods:
In vitro CYP reaction phenotyping of AFP-172 was conducted by using 12 human recombinant CYP450s (1A2, 2A6, 2B6, 2C9*1, 2C9*2, 2C19, 2D6*1, 2E1, 3A4, 4A11, 4F2, 4F3B). Eighty µmol/L of AFP-172 was incubated with each recombinant for 4 and 6 hours at 37°C and the reactions were stopped by adding acetonitrile. After extraction of the reaction mixture, they were subjected to an HPLC-MS/MS analysis to determine AFP-172 and its major metabolites (tetranor AFP-172 and dinor AFP-172), and the contributions of CYP isoforms were evaluated with a depletion of unchanged AFP-172 and formations of its metabolites.

The LC/MS/MS bioanalytical assay was adequately validated with the following results:

Quantitation range: 0.5-100 µmol/L for AFP-172, 0.05-10 µmol/L for tetranor AFP-172 and dinor AFP-172
LLOQ: 0.5 µmol/L for AFP-172, 0.05 µmol/L for tetranorAFP-172 and dinor AFP-172
Intra-day accuracy: within ±15% (LLOQ ± 20%)
Intra-day precision: within 15% (LLOQ 20%)
Stability: 72 h for post-preparative samples at auto sampler (4°C).

Reviewer's comment: *In the submitted study report, no positive controls (i.e., the known CYP450 substrate to each CYP450 evaluated) were included in the study to validate the experimental conditions. An information request was sent to the Applicant, who later confirmed that no positive control experiments were conducted in the study.*

Results:
After 6 hours incubation with each CYP, no significant AFP-172 depletion and metabolites formation was observed at the tested conditions (**Table 1**)

Table 1: Residual rate and reaction velocity

Isoform	Time	Protein conc.*	% to control			Reaction rate(pmol/min./mg)**		
			AFP-172	M-18	M-21	AFP-172	M-18	M-21
1A2	240 min.	1 mg/mL	97.4%	N.C.	N.C.	0.32	N.C.	N.C.
1A2	360 min.	1 mg/mL	98.3%	N.C.	N.C.	0.14	N.C.	N.C.
2A6	240 min.	1 mg/mL	101.1%	N.C.	N.C.	-0.13	N.C.	N.C.
2A6	360 min.	1 mg/mL	101.2%	N.C.	N.C.	-0.10	N.C.	N.C.
2B6	240 min.	1 mg/mL	98.1%	N.C.	N.C.	0.24	N.C.	N.C.
2B6	360 min.	1 mg/mL	103.3%	N.C.	N.C.	-0.27	N.C.	N.C.
2C9*1	240 min.	1 mg/mL	101.8%	N.C.	N.C.	-0.22	N.C.	N.C.
2C9*1	360 min.	1 mg/mL	100.3%	N.C.	N.C.	-0.02	N.C.	N.C.
2C9*2	240 min.	1 mg/mL	98.5%	N.C.	N.C.	0.17	N.C.	N.C.
2C9*2	360 min.	1 mg/mL	99.8%	N.C.	N.C.	0.01	N.C.	N.C.
2C19	240 min.	1 mg/mL	99.7%	N.C.	N.C.	0.03	N.C.	N.C.
2C19	360 min.	1 mg/mL	102.2%	N.C.	N.C.	-0.18	N.C.	N.C.
2D6*1	240 min.	1 mg/mL	103.0%	N.C.	N.C.	-0.39	N.C.	N.C.
2D6*1	360 min.	1 mg/mL	101.4%	N.C.	N.C.	-0.11	N.C.	N.C.
2E1	240 min.	1 mg/mL	101.4%	N.C.	N.C.	-0.17	N.C.	N.C.
2E1	360 min.	1 mg/mL	102.7%	N.C.	N.C.	-0.22	N.C.	N.C.
3A4	240 min.	1 mg/mL	84.8%	N.C.	N.C.	1.93	N.C.	N.C.
3A4	360 min.	1 mg/mL	99.4%	N.C.	N.C.	0.05	N.C.	N.C.
4A11	240 min.	100 pmol/mL	99.2%	N.C.	N.C.	0.10	N.C.	N.C.
4A11	360 min.	100 pmol/mL	93.6%	N.C.	N.C.	0.58	N.C.	N.C.
4F2	240 min.	100 pmol/mL	96.8%	N.C.	N.C.	0.42	N.C.	N.C.
4F2	360 min.	100 pmol/mL	97.0%	N.C.	N.C.	0.27	N.C.	N.C.
4F3B	240 min.	100 pmol/mL	102.1%	N.C.	N.C.	-0.28	N.C.	N.C.
4F3B	360 min.	100 pmol/mL	98.2%	N.C.	N.C.	0.16	N.C.	N.C.

* 4A11, 4F2, 4F3B(p450 content)
** 4A11, 4F2, 4F3B(pmol/min/pmol)

Sponsor's Conclusion
There were no notable reactions of the tested CYPs for metabolism of AFP-172 and it was considered that the contributions of CYPs in the in vivo human metabolism were negligible.

Reviewer's assessment and Recommendations:

Study PK032 was designed to assess the potential contribution of CYP450s in tafluprost acid metabolism. The major limitation of this study is that positive control experiments were not conducted in the study to validate the experimental conditions. Thus, the in vitro metabolism data from study PK032 should be used for internal purposes only and not used to support regulatory decisions.

4.2.7. PD comparison of tafluprost 0.0015% ophthalmic solutions: PC vs. PF

Study Number: P77550
Dates: 14 September 2005 to 05 April 2006
Study Directors and Locations: P. Juhani Airaksinen, Oulu University Hospital, Finland; Thomas Hamacher, Starnberg, Germany; Ulrich Richter, Regensburg, Germany

Title: Pharmacodynamics of tafluprost 0.0015% eye drops: a comparison between the preserved and unpreserved formulation in patients with open-angle glaucoma or ocular hypertension (Phase III)

Objectives:
The primary objective of the study was to investigate the pharmacodynamics (as expressed in IOP) of two formulations of tafluprost 0.0015% eyedrops (preserved and unpreserved) in patients with open-angle glaucoma or ocular hypertension.

The primary hypothesis for pharmacodynamics was to show that the IOP lowering effect of preserved tafluprost 0.0015% eye drops was equivalent to that of the unpreserved formulation at the end of the 4-week treatment period.

Administration and Formulations:
Tafluprost 0.0015 % preservative-free (PF, batch no. 102844) and tafluprost 0.0015 % preservative containing (PC, batch no. C000401) eye drops, one drop in the affected eye(s) at 20:00 daily for 4 weeks (PC or PF eye drops) and 4 weeks (PF or PC eye drops) in a cross-over fashion. Washout of at least 4 weeks between the treatment periods.

Methods:
This is a randomized, investigator-masked, cross-over and multicenter phase III study. A total of 43 patients were randomized in the study.

Primary pharmacodynamic variable: Change from baseline in the overall diurnal IOP at 4 weeks.
Secondary pharmacodynamic variables: Change from baseline in time-wise IOPs (8:00, 12:00, 16:00 and 20:00) at 4 weeks and change from baseline in the overall diurnal IOP and time-wise IOPs (8:00, 12:00, 16:00 and 20:00) at 1 week.
Safety variables: Adverse events, best-corrected visual acuity, biomicroscopy, ophthalmoscopy and visual field examination.

Demographic characteristics are summarized in **Table 1**.

Table 1: Demographic characteristics

Variable	N	MEAN	SD	SE	MIN	MEDIAN	MAX
Age (years)	43	65.3	10.1	1.5	35	67	85

Variable		N	%
Sex	Male	16	37.2
	Female	27	62.8
Race	Caucasian	43	100.0
Female of childbearing potential	No	26	96.3
	Yes	1	3.7
Chemical contraception	Yes	1	100.0
Pregnancy test result	Negative	1	100.0

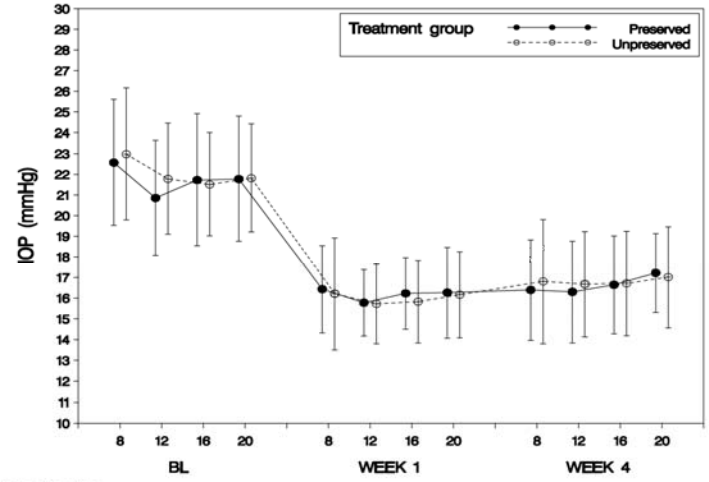
Statistical Method:

For the primary PD variable (i.e., change in IOP at Week 4), a repeated measurements analysis of covariance (RM ANCOVA) model with baseline IOP as a covariate was used to analyze the changes from baseline in the diurnal IOP at 4 weeks. The model included fixed effects for baseline, sequence, period, treatment, time, sequence by time, period by time, and treatment by time. The difference (unpreserved-preserved) and a two-sided 95% confidence interval for the difference were estimated from the RM ANCOVA model using a contrast (over all four time points). The equivalence limit was set to 1.5 mmHg. Thus, equivalence was shown if the two-sided 95% confidence interval for the difference (unpreserved-preserved) lay entirely within the equivalence range of (-1.5 mmHg, 1.5 mmHg).

Results:

The intention-to-treat (ITT) dataset for efficacy and the safety dataset included all randomized patients (N=43). The per protocol (PP) dataset for efficacy excluded 1 discontinued patient and 1 protocol violator (N=41).

As shown in **Figure 1**, for both the preserved (PC) and unpreserved (PF) formulations, a similar IOP lowering effect was seen at week 1 (at 8, 12, 16, and 20 hour post-dose). The IOP lowering effect was sustained from week 1 to week 4. For both ITT and PP datasets, PF and PC formulations were equivalent in IOP reduction at Week 4.



BL = Baseline
Source: Table 14.2.1.1 and Figure 14.2.1

Figure 1: The mean (± SD) intraocular pressure (IOP) during the study (worse eye)

Table 2: The estimated overall treatment difference (unpreserved-preserved) at 4 weeks

Week 4	RM ANCOVA			
Dataset	Difference (mmHg)	Lower 95% CI	Upper 95% CI	P-value
ITT efficacy (N=43)	0.01	-0.46	0.49	0.96
PP efficacy (N=41)	-0.05	-0.52	0.42	0.83

Source: Table 14.2.2

A total of 21 adverse events (20 ocular and 1 non-ocular) were reported by 11 (25.6%) patients for the unpreserved formulation, whereas a total of 10 adverse events (7 ocular and 3 nonocular) were reported by 7 (16.7%) patients for the preserved formulation. There were neither serious adverse events nor withdrawals due to adverse events in this study.

Sponsor's Conclusion
The study in patients with open angle glaucoma or ocular hypertension was conducted to investigate the pharmacodynamics (as expressed in IOP) of the preserved and unpreserved formulation of tafluprost 0.0015% eye drops and to show that the IOP reduction between the two formulations is equivalent at the end of the 4-week treatment period. Hereby it can be concluded, that removal of preservative benzalkonium chloride from the tafluprost ophthalmic formulation, has no effect on the IOP control.

Reviewer's assessment and Recommendations:

Study P77550 adequately compared the efficacy (IOP reduction at Week 4) following topical ocular administration of PF vs. PC tafluprost 0.0015% ophthalmic solution to patients. The sponsor's conclusion regarding the interchangeability (in terms of IOP reduction) between the two formulations is valid.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YONGHENG ZHANG

07/18/2011

Phil: Besides in the exe summary, I added the dosage & administration in the title page as well. For the labeling, I decided to remove (b) (4)

PHILIP M COLANGELO

07/20/2011

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA:	202-514
Drug Name:	Tafluprost 0.0015% ophthalmic solution
Applicant:	MERCK & CO., INC.
Submission Date:	January 7, 2011
Filing Date:	March 8, 2011
PDUFA Date:	November 7, 2011
OCP Primary Reviewer:	Yongheng Zhang, Ph. D.
OCP Team Leader:	Kimberly Bergman, Pharm D.

QUESTION	***YES***	***NO***	***NA***	***COMMENTS***
Fileability: ***Is the Clinical Pharmacology section of the application fileable?*** ***(if 'NO', please comment as to why it is not fileable)***	***YES***			
Fileability Review Components				
1. Is the clinical pharmacology section of the NDA organized in a manner to allow substantive review to begin (including a table of contents, proper pagination, reference links, etc.)?	☒	☐	☐	
2. Are the clinical pharmacology studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?	☒	☐	☐	Six Ph 1 studies with PK as an endpoint including #77551 (PF/PC) and #15-005 (PC); Dose ranging explored in two Ph 2 studies (# 15001 & 15002); Five Ph 3 studies including PF/PC bridging study (# 77550)
3. If multiple formulations were used in the clinical development of the product, does the NDA contain appropriate biopharmaceutics information to allow comparison between the clinical development and to-be-marketed product(s) (i.e. pivotal BE)?	☒	☐	☐	See additional comments below
4. If unapproved products or altered approved products were used as active controls, was bioequivalence to the approved product demonstrated?	☐	☐	☒	
5. Are complete and relevant bioanalytical reports included in the NDA submission?	☒	☐	☐	Assay validation report (# 6776-110) provided for tafluprost acid (LLOQ=10 pg/mL). Another assay validation report (# STN 29/003389) also provided for both tafluprost and tafluprost acid (LLOQ=0.2 and 0.1 ng/mL, respectively)
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	☐	☐	☒	

7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	☒	☐	☐	Individual concentration data submitted in concen.xpt

Additional comments:
PF: preservative free; PC: preservative containing
TBM: the to-be-marketed formulation, i.e., tafluprost 0.0015% PF ophthalmic solution.

Most clinical studies including two Phase 3 pivotal studies (# P15003 and # P74458) were conducted using tafluprost PC formulations. PF and PC formulations were bridged by conducting an 8-day PK comparison study (Ph1 #77551 –*Table below*) and a 4-week efficacy comparison study (Ph3 #77550 –*Figure below*).

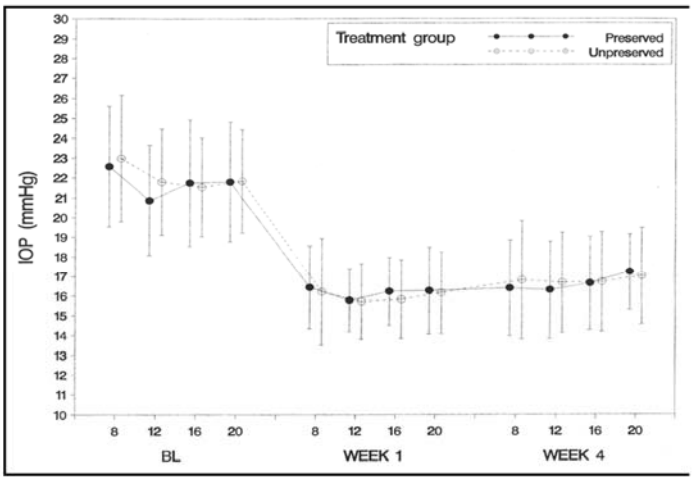
Pharmacokinetic Parameters From Study 77551 of Tafluprost Acid in Plasma After Application of One Drop of Preserved or Unpreserved 0.0015% Ophthalmic Solution on Each Eye in Adult Healthy Volunteers (Mean ± SD for $AUC_{0\text{-last}}$ and C_{max}; Median and Range for t_{max}) at Day 1 and Day 8

Day of Treatment Period (n)	$AUC_{0\text{-last}}$(pg*min/ml)	C_{max} (pg/ml)	t_{max} (min) (min – max)
Preserved			
Day 1 (n=16)	405.9±395.2[a]	24.42±15.76[a]	10 (10-15)
Day 8 (n=16)	581.1±529.9[b]	31.43±19.53[b]	10 (5-15)
Unpreserved)			
Day 1 (n=16)	394.3±286.4[a]	26.16±10.35	10 (5-15)
Day 8 (n=16)	431.9±457.8[b]	26.61±18.02[b]	10 (5-15)

[a] Differences between the preserved or unpreserved formulations were not statistically significant on Day 1 (p=0.600 and 0.529 for $AUC_{0\text{-last}}$ and C_{max}, respectively).
[b] Differences between the preserved or unpreserved formulations were not statistically significant on Day 8 (p=0.462 and 0.294 for $AUC_{0\text{-last}}$ and C_{max}, respectively).

Table 5 and Table 6 in study report 77551

Intraocular Pressure at all Time Points in Patients Treated Once Daily With Preservative-Containing/Preservative-Free 0.0015% Tafluprost Ophthalmic Solution in Study 77550. (Mean±SD)



BL=baseline

Figure 1 in [Ref. 5.3.4.2: P77550]

The results of Study 77550 demonstrate that the IOP-reducing effect of the preservative-free formulation containing 0.0015% tafluprost is equivalent with the corresponding preservative-containing formulation as defined in the protocol.

OCP Primary Reviewer _____ Date _____

OCP Team Leader _____ Date _____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YONGHENG ZHANG
02/16/2011

KIMBERLY L BERGMAN
02/16/2011