CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206185Orig1s000

NON-CLINICAL REVIEW(S)

Response to CR letter - Among other requests, the CR letter asked the sponsor to provide a safety update. The sponsor conducted a literature search of clinical as well as nonclinical data for the period from March 17, 2014 to date. Only one nonclinical reference was considered to provide potentially new safety information. In a study in rabbits after monotherapy of different commercial PG analogs, dry eye symptoms occurred in eyes treated with latanoprost (which contains the highest concentration of BAK). The authors concluded that the study findings confirm that the in vivo toxic effect of commercial PG analogs on corneal epithelial barrier function is dependent on BAK concentrations. As a note, the proposed Xelpros formulation does not contain BAK. There are no new changes to the proposed label except for the use of "Xelpros" instead of "Latanoprost ophthalmic (b) (4)" in Section 8.1. There are no nonclinical issues.

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/s/

MARIA I RIVERA
04/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ADDENDUM TO PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206-185
Supporting document/s:	1 (Original NDA)
	8 (Labeling/Package Insert Draft)
Applicant's letter date:	January 31, 2014 (SD # 1)
	April 30, 2014 (SD # 8)
CDER stamp date:	January 31, 2014 (SD # 1)
	April 30, 2014 (SD # 8)
Product:	Xelpros (latanoprost) 0.005% Ophthalmic (b) (4)
Indication:	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Applicant:	Sun Pharma Advanced Research Company (SPARC) Ltd
Review Division:	Transplant and Ophthalmology Products
Reviewer:	María I. Rivera, PhD
Supervisor/Team Leader:	Lori E. Kotch, PhD
Division Director:	Renata Albrecht, MD
Project Manager:	Diana Willard

This addendum is to provide additional clarification to Section 1. Executive Summary of the NDA nonclinical review (second paragraph on page 4) regarding which data was relied upon for NDA approval.

SPARC used a combination of original studies and reliance on a listed drug (Xalatan®) to provide nonclinical support for NDA Application 206-185, as follows:

1. To support the safety of the active pharmaceutical ingredient, latanoprost, SPARC relied on FDA's prior findings of safety and effectiveness for Xalatan®, as summarized in the most current labeling (revised August 2012).

2. To evaluate the systemic and local ocular toxicities of the new latanoprost formulation, SPARC conducted original studies, including repeated-dose ocular toxicity studies of up to 180-day duration in dogs and rabbits. Ocular-route studies included additional study arm(s) to assess the local and systemic safety of the novel ocular excipient (b) (4) administered alone.

3. To provide additional support for the systemic safety of (b) (4) SPARC conducted repeated-dose oral toxicity studies of (b) (4) in rats of up to 180-day duration. In addition, SPARC provided an extensive battery of systemic toxicity studies conducted by (b) (4) Because SPARC provided the full study reports for (b) (4) conducted studies, a right of reference was not needed to access these data.

4. The publications provided by the applicant to support the safety of (b) (4) (b) (4) were not essential for approval, since the original study data provided to support safety of the excipient were sufficient.

Additionally, corrections are made to the wording contained in Section 4.2 *Secondary Pharmacology* (page 11) and Section 11 (pg 39) of the original review. The document from Hellwig (1984) was incorrectly referred to as a publication from (b) (4) but is actually a study report. References to this document should be changed, as follows:

1. Section 4.2: The original review states *"The applicant included a **publication** from (b) (4) that summarizes trial studies conducted by (b) (4) between December 1983 and May 1984 in beagle dogs (Hellwig-1984; EDR Module 4.2.1.3)."*

   This sentence should be modified to read *"The applicant included a **study report** from (b) (4) that summarizes trial studies conducted by (b) (4) between December 1983 and May 1984 in beagle dogs (Hellwig-1984; EDR Module 4.2.1.3)."*

2. Section 11: The original review states *"In a **published** study conducted by (b) (4) in beagle dogs, (b) (4) led to an anaphylactoid reaction and an increase in the release of plasma histamine."*

   This sentence should be modified to read *"In a **study** conducted by (b) (4) in beagle dogs, (b) (4) led to an anaphylactoid reaction and an increase in the release of plasma histamine."*

CC list:
D. Willard/PM
R. Lloyd/MO

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/s/

MARIA I RIVERA
11/24/2014

LORI E KOTCH
11/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206-185
Supporting document/s:	1 (Original NDA)
	8 (Labeling/Package Insert Draft)
Applicant's letter date:	January 31, 2014 (SD # 1)
	April 30, 2014 (SD # 8)
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Indication:	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Applicant:	Sun Pharma Advanced Research Company (SPARC) Ltd
Review Division:	Transplant and Ophthalmology Products
Reviewer:	María I. Rivera, PhD
Supervisor/Team Leader:	Lori E. Kotch, PhD
Division Director:	Renata Albrecht, MD
Project Manager:	Diana Willard

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 206-185 are owned by SPARC or are data for which SPARC has obtained a written right of reference. Any information or data necessary for approval of NDA 206-185 that SPARC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 206-185.

TABLE OF CONTENTS

Table of Tables

1 Executive Summary

1.1 Introduction

SPARC seeks approval of Latanoprost Ophthalmic [redacted] 0.005%, which is intended for the same dosage (1 drop QD or 1.5 µg/day) and administration (once daily in the evening) as that of the approved Listed Drug (LD) Xalatan® (NDA 20-597), for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. The new formulation contains an excipient, [redacted] which has not been previously approved in an ophthalmic product in the United States.

SPARC is relying on FDA's prior decision of the efficacy and safety of latanoprost, as summarized in the most current labeling (revised August 2012). In addition, SPARC performed repeated-dose ocular toxicity studies of up to 180-day duration in dogs and rabbits to evaluate the systemic and local ocular toxicities of the new formulation. To evaluate the ocular safety of [redacted] these studies included an additional arm(s) using this excipient. Systemic safety of [redacted] was evaluated in repeated-dose oral toxicity studies of [redacted] in rats of up to 180-day duration. In addition, SPARC used the extensive battery of systemic toxicity studies conducted by [redacted] At the Pre-IND meeting (IND 102,842), FDA agreed that, provided SPARC had appropriate right of reference or access to the reports, these studies appeared sufficient to support the balance of the requirements for an eventual NDA.

1.2 Brief Discussion of Nonclinical Findings

In dogs, findings included an increased incidence of mild to moderate scleral congestion compared to controls (saline, placebo, and [redacted] and miosis at all Latanoprost Ophthalmic [redacted] 0.005% doses (QD, BID, and QID). The miosis was an expected pharmacological effect. These findings reversed during the recovery period. There was no ocular NOAEL. No adverse systemic findings were observed in any of the Latanoprost Ophthalmic [redacted] 0.005% dose groups or [redacted] alone arm (0.25% QID).

In rabbits, mild lacrimation and redness in the conjunctiva were observed at the latanoprost high dose (Latanoprost Ophthalmic [redacted] 0.005%, QID). These findings reversed during the recovery period. There were no adverse systemic findings. The NOAEL was the mid dose, Latanoprost Ophthalmic [redacted] 0.005% BID. No ocular or adverse systemic findings were observed in the [redacted] alone arm (0.25% QID).

Exposure margins (based on total dose administered per eye) for ocular effects ranged between 2-3-fold. The ocular findings observed in the nonclinical studies are consistent with those observed in the clinical trials. Ocular findings in the clinic included ocular hyperemia, conjunctival hyperemia, and eye discharge. The sensitivity for the occurrence of miosis appears to be species dependent. Its occurrence in human following treatment with latanoprost is not common.

Intravenous administration of [redacted] (b) (4) 0.25% to rats resulted in lipid accumulation in the sinus endothelial cells in the liver and spleen and an increase in the number and size of small granulomas (containing lipid droplets with brown pigment granules) in the liver. The lipid deposits were presumed to represent denaturation products of stearic acid.

Intravenous administration of [redacted] (b) (4) to beagle dogs resulted in signs of an allergic reaction (pruritus, erythema, wheals) at doses ≥50 mg/kg which resolved within 15-60 min postdose.

In an embryofetal development toxicity study in rabbits, there was a significant increase (2.4-fold) in the number of resorptions and post-implantation loss and a decrease in live fetuses at the high [redacted] (b) (4) dose of 464 mg/kg/day IV administered during organogenesis. In addition, fetal incidences of misaligned sternebrae and total skeletal variations were increased at this dose.

The exposure margins (based on mg/m^2) for systemic toxicities observed after IV dosing with [redacted] (b) (4) are over 1,600X; those for the observed embryotoxicity are over 27,000X. The magnitude of the exposure margins indicate that similar findings are unlikely to be observed in the clinic at the intended clinical dosing regimen.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The reviewer's suggested deletions from the applicant's proposal are struck out and suggested additions are in bold italic text.

8.1 Pregnancy

Applicant-Proposed language:

[redacted] (b) (4) Pregnancy Category C

Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Latanoprost ophthalmic [redacted] (b) (4) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reviewer's recommended edits:

(b) (4) Pregnancy Category C

No other edits are recommended for the Pregnancy Section.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Applicant-Proposed language:

(b) (4)

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 µg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively.

Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.

Reviewer's recommended edits:

(b) (4)

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 µg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively.

Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed in vitro with human lymphocytes. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative.

Latanoprost has not been found to have any effect on male or female fertility in animal studies.

(b) (4)

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 130209-82-4

Generic Name: Latanoprost

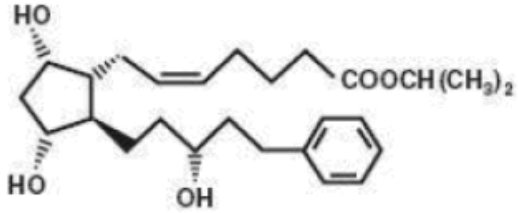
Chemical Name:

(5*Z*)-7-[(1R,2R,3R,5S)- 3,5-dihydroxy-2-[(3R)-3-hydroxy- 5-phenylpentyl]cyclopentyl]-5-heptenoic acid 1-methylethyl ester

Isopropyl-(*Z*)-7[(1R,2R,3R,5S) 3,5-dihydroxy-2-[(3R)-3-hydroxy-5 phenylpentyl]cyclo-pentyl]-5-heptenoate

Molecular Formula/Molecular Weight: $C_{26}H_{40}O_5$/432.61 g/mol

Structure:



Pharmacologic Class: Prostaglandin analog; prostanoid F2α receptor agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 102,842 (Latanoprost Ophthalmic (b) (4) 0.005%)
NDA 20-597 (Xalatan®; latanoprost ophthalmic solution, 0.005%; approved 1996)

DMF # (b) (4) (latanoprost) (b) (4)

2.3 Drug Formulation

The components of Latanoprost Ophthalmic (b) (4) 0.005%, their function, and quality are provided in Table 1.

Table 1: Composition of Latanoprost Ophthalmic (b) (4) 0.005%

Component	Amount (per mL)	% w/v	Function	Reference to Quality Standards
Latanoprost	0.05	0.005	Active	In house
Potassium sorbate	4.70	0.47	Preservative	NF
Boric acid	(b) (4)	(b) (4)	(b) (4)	NF
Edetate disodium				USP
Castor oil				USP
(b) (4)				Ph.Eur.
Propylene glycol				USP
Sodium borate				NF
Hydrochloric acid				NF
Sodium hydroxide				NF
Water for injection				USP
(b) (4)				

(b) (4)

(b) (4). In addition, repeated-dose systemic toxicology studies of up to 26 weeks duration in rats and 4 weeks in dogs, safety pharmacology studies, genotoxicity studies, reproductive and developmental toxicity studies, and studies to determine the potential for skin sensitization, ocular and dermal irritancy, and hemolysis were completed in order to qualify the safety of (b) (4) as an excipient.

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Latanoprost Ophthalmic (b) (4) 0.005% (50 µg/mL) is indicated for the reduction of elevated intraocular pressure (IOP) in subjects with open-angle glaucoma or ocular hypertension. The proposed dosing regimen is one drop (1.5 µg, assuming a (b) (4) µL drop volume) per day. This dosing regimen is the same as the approved listed drug Xalatan® (latanoprost ophthalmic solution, 0.005%; Pharmacia and Upjohn; approved in 1996).

2.7 Regulatory Background

A pre-IND meeting (IND 102,842) was held on September 16, 2008. In this meeting, the applicant was told of the need to conduct nonclinical studies to qualify the excipient (b) (4) The Division agreed that based on technical infeasibility to detect (b) (4) as an intact product, measurement of systemic exposure or eye tissue distribution after ocular administration was not required. There were no nonclinical questions for the pre-NDA meeting held on February 20, 2013.

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology

- Comparative *In Vivo* Efficacy Study of 0.005% w/v Latanoprost Ophthalmic (b) (4) (Microemulsion) – Sun Product (Batch No. CB-12364-070) vs. Xalatan® (Batch No. ME1036) on Intraocular Pressure in Healthy Male Beagle Dogs – Crossover Study (Study # BRP/08/002)

PK/ADME

- Comparative Tissue Distribution and Pharmacokinetic Study of Latanoprost Ophthalmic (b) (4) – Sun Product (Batch No. JK82671) versus Xalatan® (Batch No. KF53978) in Male NZW Rabbit (Study # BRP_09_165)
- Comparative Plasma and Ocular Tissue Pharmacokinetic Study of Latanoprost Ophthalmic (b) (4) 0.005% w/v, 2.5 mL (Microemulsion) – SPARC Ltd. Product (Batch No. JK82671) versus Xalatan®, 0.005% w/v (Batch No. LA54023) in Male NZW Rabbits (Study # BRP_09_420)

Repeat-Dose Toxicity:

- A 30-Day Repeated-Dose Range Finding Ocular Toxicity Study of Latanoprost in Beagle-Dogs with Toxicokinetics Evaluation (Study # BRT/09/026; GLP; Module 4.2.3.2)
- A 180-Day Repeated-Dose Ocular Toxicity Study of Latanoprost Ophthalmic (b) (4) in Beagle Dogs with Toxicokinetic Evaluation (BRT_09_075)
- A 180-Day Repeated Dose-Ocular Toxicity Study of Lantanoprost in New Zealand White Rabbits with Toxicokinetic Evaluation (BRT/09/038)
- A 180-Day Repeated-Dose Oral Toxicity Study of (b) (4) in Wistar Rats (BRT/09/023)

Note: *In vivo* efficacy study in dogs (Study # BRP-08-002), 14-day rabbit ocular toxicity study (Study # BRT-07-145), 14-day rabbit dose-ranging ocular study (Study # BRT-08-100), and 30-day rabbit ocular toxicity study (Study # BRT-09-015) to evaluate the ocular and systemic safety of Latanoprost Ophthalmic (b) (4) 0.005% and (b) (4) (b) (4) 0.25%, and systemic route studies to qualify (b) (4) were previously reviewed under the initial IND by Theresa Allio, PhD (review filed in DARRTS on 2-23-2010).

The systemic route studies with (b) (4) reviewed under the initial IND included safety pharmacology, single-dose by the intravenous (IV), intraperitoneal (IP), and oral (PO) routes of administration in dogs, rabbits, and mice, repeated-dose by the PO and IV routes of administration (up to 4 weeks in dogs and up to 3-months in rats), genetic toxicity, and reproductive toxicity. In addition, studies to evaluate (b) (4) potential for eye irritation, dermal irritation, skin sensitization, and hemolysis were conducted.

3.2 Studies Not Reviewed

- A 7-Day Pilot Study of Latanoprost in Beagle Dogs by Ocular Route (Study # BRT/09/016)

3.3 Previous Reviews Referenced

- Pre-IND 102,842 (Filed in DARRTS on 10-16-2008)
- IND 102,842 (Filed in DARRTS on 2-23-2010)

4 Pharmacology

4.1 Primary Pharmacology

Latanoprost is a prostaglandin analog and prostanoid F2α receptor agonist. It is a prodrug which is hydrolyzed *in vivo* to latanoprost acid, a derivative of prostaglandin F2α. Latanoprost is believed to reduce the intraocular pressure (IOP) by increasing the outflow of the aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow, thereby decreasing the pressure within the eye and reducing the risk of nerve damage and potential blindness associated with glaucoma.

A study was conducted to compare the efficacy of Latanoprost Ophthalmic (b) (4) 0.005% (microemulsion; batch # CB-12364-070) to that of Xalatan® on intraocular pressure in healthy male beagle dogs (Study # BRP/08/002). Six dogs were used in this study. In Period I of the study, Latanoprost Ophthalmic (b) (4) 0.005% was administered to the left eye and Xalatan® to the right eye of the same dog once daily (30 µL/eye) from Day 3 to Day 12. After a 10-day washout period, the test and reference item were applied to the opposite eye as originally administered (Period II).

Intraocular pressure, pupillary diameter, blepharospasm, conjunctival hyperemia and aqueous flare were evaluated. No significant difference was observed in mean IOP reduction and pupillary diameter reduction. The maximal decrease of IOP occurred between 6 to 12 hours postdose for both products. The study report states that mild conjunctival hyperemia (score 1) was detected in several eyes for both test articles, and that aqueous flare and blepharospasm were not detected (data not shown).

4.2 Secondary Pharmacology

The applicant included a publication from (b) (4) that summarizes trial studies conducted by (b) (4) between December 1983 and May 1984 in beagle dogs (Hellwig-1984; EDR Module 4.2.1.3). The various trial studies indicated that (b) (4) leads to an anaphylactoid reaction and an increase in the release of plasma histamine. A dose-response relationship was observed for the increase in the levels of plasma histamine. However, the measured histamine release did not correspond with the observations of clinical signs in each case. A (b) (4) dose of 25 mg/kg IV (administered 19 times; dosing frequency not specified) was the NOAEL in this study, as there were no clinical signs or histamine release at this dose. (b) (4) (undiluted 0.1 mL/kg-single IV administration), a surfactant known to induce histamine release and an anaphylactoid reaction, showed an increase in plasma histamine 10-fold higher than that of (b) (4).

This study was previously reviewed under the Initial IND by Dr. Theresa Allio.

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4.3 Safety Pharmacology

SPARC did not perform any safety pharmacology studies with Latanoprost Ophthalmic (b) (4) 0.005%. SPARC is relying on safety pharmacology studies of latanoprost conducted for the approval of Xalatan® (NDA 20-597). The applicant conducted comparative PK data (see Section 5.1 below) and the observed differences in plasma levels were not considered of toxicological significance. Additionally, the safety pharmacology profile after ocular administration of latanoprost 0.005% to humans is well established based on the long history of use since its approval in 1996.

The following studies were conducted to characterize the safety profile of (b) (4). These studies were previously reviewed under the Initial IND by Dr. Theresa Allio.

Table 2: Summary of Safety Pharmacology Studies Conducted with (b) (4) (b) (4)

Study	Study #	Test system	Dose	Results
CNS	X-010-31/FP-03/96 (non-GLP)	Mouse, NMRI (10 males/group)	Single IV dose of 500 mg/kg, or single oral dose of 1000 mg/kg	No adverse findings
Cardiovascular and respiratory	FP/S-03/95 (non-GLP)	Dog, Montrel (3 males)*	Single oral dose of 500 mg/kg (gelatin capsules), followed by a single oral dose of 1000 mg/kg after a 14-day washout period; 0.5% tylose in gelatin capsules as control	No adverse findings

* Correction from initial IND review: only 3 animals were used and administered both doses after a washout period. The same 3 animals also received 1.0 mL/kg 0.5% tylose (5-hydroxyethylcellulose) in gelatin capsules (control). The report does not specify the time at which the control capsules were administered.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Comparative Tissue Distribution and Pharmacokinetic Study of Latanoprost Ophthalmic (b) (4) **– Sun Product (Batch No. JK82671) versus Xalatan® (Batch No. KF53978) in Male NZW Rabbit (Study # BRP_09_165)** – Latanoprost Ophthalmic (b) (4) 0.005% was instilled topically to the right eye and Xalatan® was instilled to the left eye of the same rabbit (n=6). Each animal received a single dose (30 µL) of each test article. Distribution of latanoprost (presumed to be the free acid) to the conjunctiva, cornea, aqueous humor, iris, lens, ciliary body, vitreous humor, retina, sclera, and eye lid were measured at 0.25, 0.5, 1, 4, 6 and 24 hours post instillation. For both test articles, the rank order of distribution (based on AUC_{0-t}) was cornea > sclera = eyelid > conjunctiva > iris/ciliary body. There was no distribution to the lens by any product or to the vitreous by Xalatan®. Levels in the aqueous humor after the administration of Latanoprost Ophthalmic (b) (4) 0.005% were 16-fold (C_{max}) or 260-fold (AUC) higher than those in the vitreous (not included in the rank order because of different units used, i.e., ng/g vs. ng/mL). The conclusion in the study report indicated that in overall the ocular distribution seemed to be similar between both products. However, this reviewer's assessment is that some differences were observed particularly in the iris/ciliary body, retina, eyelid, aqueous humor, and vitreous humor (see ratio of Xalatan®/Latanoprost Ophthalmic (b) (4) 0.005% in Table 3). However, the reviewer agrees with the applicant that based on one animal/timepoint, a definitive conclusion cannot be reached in this study.

Table 3: Ratio of Xalatan®/Latanoprost Ophthalmic [redacted] (b) (4) 0.005% in Ocular Tissues after Ocular Administration to Rabbits (Pilot Study)

	Iris and Ciliary Body	Conjunctiva	Cornea	Retina	Lens	Sclera	Eye lid	Aqueous Humor	Vitreous Humor
Cmax	1:0.84	1:1.07	1:1.05	1:2.06	---	1:1.00	1:0.97	1:0.97	---
AUC_{0-t}	1:0.77	1:1.09	1:0.82	1:0.96	---	1:1.28	1:0.64	1:2.48	---
$AUC_{0-inf.}$	1:0.62	1:1.08	---	1:0.80	---	1:1.19	1:0.66	---	---

Comparative Plasma and Ocular Tissue Pharmacokinetic Study of Latanoprost Ophthalmic [redacted] (b) (4) 0.005% w/v, 2.5 mL (Microemulsion) – SPARC Ltd. Product (Batch No. JK82671) versus Xalatan®, 0.005% w/v (Batch No. LA54023) in Male NZW Rabbits (Study # BRP_09_420) - Latanoprost Ophthalmic [redacted] (b) (4) 0.005% or Xalatan® was instilled topically to both eyes of each rabbit (18 rabbits/group). Each animal received a single dose (30 µL; 1.5 µg/eye) of each test article on each eye. Blood was collected and distribution of latanoprost free acid to the conjunctiva, cornea, aqueous humor, iris/ciliary body, lens, vitreous humor, retina, sclera/choroid, optic nerve, and eye lid were measured at 0.25, 0.5, 1, 4, 6 and 24 hours post instillation (3 rabbits/timepoint).

Plasma levels were low for both test items (Table 4). C_{max} was lower, AUC was higher and half-life was longer for Latanoprost Ophthalmic [redacted] (b) (4) 0.005% compared to Xalatan®. Based on the low plasma levels observed (pg/mL range), and lack of a safety concern in the repeated-dose ocular toxicity studies, these differences are not considered to be of toxicological relevance.

Table 4: Mean Plasma Pharmacokinetic Profile of Latanoprost Free Acid after Ocular Administration of Latanoprost Ophthalmic [redacted] (b) (4) 0.005% and Xalatan®

Dose: 1.5 µg/eye Tissue	Dose Group	Cmax (pg/mL)	AUC_{0-t} (hr*pg/mL)	AUC_{0-inf} (hr*pg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
Plasma#	Test Item - Latanoprost Ophthalmic [redacted] (b) (4) (JK82671)	174.1	275.788	334.242	0.25	2.222
	Reference Item - Xalatan® (LA54023)	217.2	100.346	105.455	0.25	0.203

Dose considered for plasma samples for pharmacokinetics is 3 µg

Based on AUC_{0-t}, the rank order of latanoprost free acid distribution observed with Latanoprost Ophthalmic [redacted] (b) (4) 0.005% was cornea > eyelid > sclera/choroid > conjunctiva > iris/ciliary body = retina > lens = optic nerve (Table 5). That for Xalatan® was cornea > eyelid > conjunctiva > sclera/choroid > iris/ciliary body > retina > lens > optic nerve. For both test and LD, latanoprost free acid levels in the aqueous humor were 10 to16-fold (C_{max}) and 3.5 to 22-fold (AUC_{0-t}) higher than those in the vitreous (not included in the rank order because of different units used, i.e., ng/mg vs. ng/mL).

Table 5: Mean Pharmacokinetic Parameters for Latanoprost Ophthalmic (b) (4) 0.005% and Xalatan® in Ocular Tissues after Topical Ocular Administration to Rabbits

Tissue	Dose Group	C_{max} (ng/mg)	AUC_{0-t} (hr*ng/mg)	AUC_{0-inf} (hr*ng/mg)	T_{max} (hr)	$T_{1/2}$ (hr)	AUC_{0-inf} ratio (tissue/aqueous humor)
Aqueous Humor#	Test Item - Latanoprost Ophthalmic (b) (4) (JK82671)	39.197	126.441	133.141	1.00	1.436	1.00
	Reference Item - Xalatan® (LA54023)	37.477	112.039	119.624	1.00	1.499	1.00
Vitreous Humor#	Test Item - Latanoprost Ophthalmic (b) (4) (JK82671)	2.375	35.702821	*	6.00	*	#VALUE!
	Reference Item - Xalatan® (LA54023)	3.792	5.11615	*	6.00	*	#VALUE!
Conjunctiva	Test Item - Latanoprost Ophthalmic (b) (4) (JK82671)	0.114	0.29	0.298	0.25	5.644	0.00
	Reference Item - Xalatan® (LA54023)	0.148	0.483	0.503	0.25	6.390	0.00
Cornea	Test Item - Latanoprost Ophthalmic (b) (4) (JK82671)	0.722	2.212	2.226	0.50	3.691	0.02
	Reference Item - Xalatan® (LA54023)	0.655	2.07	2.079	0.25	3.353	0.02
Eye Lid	Test Item - Latanoprost Ophthalmic (b) (4) (JK82671)	0.100	0.728	2.263	0.25	41.445	0.02
	Reference Item - Xalatan® (LA54023)	0.177	1.089	2.025	0.25	27.414	0.02
Iris & Ciliary Body	Test Item - Latanoprost Ophthalmic (b) (4) (JK82671)	0.039	0.077	0.083	0.50	1.466	0.00
	Reference Item - Xalatan® (LA54023)	0.075	0.093	0.105	0.25	2.075	0.00
Lens	Test Item - Latanoprost Ophthalmic (b) (4) (JK82671)	0.008	0.003	0.004	0.25	2.209	0.00
	Reference Item - Xalatan® (LA54023)	0.008	0.004	0.008	0.25	3.983	0.00
Optic nerve	Test Item - Latanoprost Ophthalmic (b) (4) (JK82671)	0.009	0.003	*	1.00	*	#VALUE!
	Reference Item - Xalatan® (LA54023)	0.003	0.002	0.006	0.25	1.598	0.00
Retina	Test Item - Latanoprost Ophthalmic (b) (4) (JK82671)	0.018	0.073	0.084	0.25	9.342	0.00
	Reference Item - Xalatan® (LA54023)	0.019	0.052	0.056	0.25	1.822	0.00
Sclera/choroid	Test Item - Latanoprost Ophthalmic (b) (4) (JK82671)	0.177	0.361	0.383	0.25	7.626	0.00
	Reference Item - Xalatan® (LA54023)	0.095	0.323	0.328	0.25	4.545	0.00

* Value not estimable
#VALUE! Value not estimable
ng/mL for C_{max} and hr*ng/mL for AUC_{0-t} and AUC_{0-inf}

Based on AUC_{0-inf}, the main differences in ocular tissue distribution include higher levels of latanoprost free acid in the vitreous, optic nerve and retina and lower levels in the conjunctiva, iris/ciliary body and lens observed in Latanoprost Ophthalmic (b) (4) (b) (4) 0.005% compared to Xalatan®. The ratios of Xalatan®/Latanoprost Ophthalmic (b) (4) 0.005% are shown in the table below:

Table 6: Ratio (Latanoprost Ophthalmic (b) (4) 0.005%/Xalatan®) in Ocular Tissues after Ocular Administration to Rabbits

Tissue	T/R Ratio	
	C_{max}	AUC_{0-inf}
Plasma	0.80	3.17
Aqueous Humor	1.05	1.11
Vitreous Humor	0.63	6.98*
Conjunctiva	0.77	0.59
Cornea	1.10	1.07
Eye Lid	0.56	1.12
Iris & Ciliary Body	0.52	0.79
Lens	1.00	0.50
Optic Nerve	3.00	1.50*
Retina	0.95	1.50
Sclera/choroid	1.86	1.17

T/R=test/reference

* Considered AUC_{0-t} since AUC_{0-inf} values were not estimable

6 General Toxicology

6.1 Single-Dose Toxicity

Single-dose studies by the PO, IV, and IP routes of administration were conducted with (b) (4) in several species. These studies were previously reviewed under the initial IND. The main findings are summarized in Table 7.

Note: The doses in Table 7 are given in mg/kg except were they are specified as mL/kg. Based on the information provided in the study report (Wesenberg 1980), it was not possible to calculate the equivalent in mg/kg.

Table 7: Summary of Single-Dose Systemic Route Toxicity Studies Conducted with (b) (4)

Species, Strain	Method of Administration	Doses (mg/kg)	No/sex/group	Observed Maximum Nonlethal Dose (mg/kg)	LD_{50} values (mg/kg)	Study/Report Number or Source
Mouse, NMRI	p.o. (gavage)	20 mL/kg	10 female/group	20 mL/kg	> 20 mL/kg	*Wesenberg 1980*, (b) (4)
Mouse, NMRI	i.v.	1000, 2150, 3160, 5000, 6810	5/sex/group	Male: 1000 Female: 2150	Male: 3160 Female: 5000	*80/523 Rat/IV*, (b) (4)
Mouse, NMRI	i.p.	5, 7.5, 10 mL/kg	10 female/group	5 mL/kg	8.49 mL/kg	*Wesenberg 1980*, (b) (4)
Rat, Sprague-Dawley	p.o. (gavage)	20 mL/kg	10/sex/group	> 20 mL/kg	> 20 mL/kg	*Wesenberg 1980*, (b) (4)
Rat, Sprague-Dawley	i.v.	1000 and 1470	5/sex/group	Male: not established Female: 1000	Male: 1212 Female: 1327	*80/523 Rat/IV*, (b) (4)
Rabbit, bastard	i.v.	681, 1000, 1470	2/sex/group	681	Between 1000 and 1470 for both sexes	*80/523 IV* Kaninchen, (b) (4)
Dog, Beagle	i.v.	56.2, 215, 464, 825, 1470, 2150, 3160	1/sex/group	3160	> 3160 for both sexes	*80/523 Beagle*-Hund, (b) (4)

Depending on the dose, clinical signs observed in these studies included dyspnea, panting, lateral position, abdominal position, somnolence, skin hyperemia, vomiting, apathy, retching reflex, foamy mouth, defecation, staggering, tonus of the jaws and tonus with stretching, and/or opisthotonus. Symptom duration was dependent on dose, with resolution observed 2 to 4 hours postdose. Other symptoms (Study # 80/523 Rat/IV) included spastic gait, paresis, saltatory spasms, and/or tonic and clonic spasms in mice. The study report did not indicate if these symptoms showed resolution. In animals found dead, clinical signs included generalized congestive hyperemia, edematized lungs, and/or acute dilatation and acute congestive hyperemia in the heart. A NOAEL was identified in dogs at 56.2 mg/kg IV (Study # 80/523/Beagle).

6.2 Repeat-Dose Toxicity

Ocular Route Studies

Repeated-dose ocular toxicity studies of 14-day (non-GLP) and 30-day (GLP) duration in New Zealand White (NZW) rabbits were previously reviewed under the initial IND. The ocular and systemic safety after ocular administration of Latanoprost Ophthalmic (b) (4) (microemulsion), 0.005% and (b) (4) 0.25% were evaluated. The main findings are summarized in Table 8.

Table 8: Summary of Subchronic Ocular Toxicity Studies of Latanoprost Ophthalmic (b) (4) 0.005% and (b) (4) 0.025% Conducted in Rabbits

Study	Study #	Dose	Results
14 day NZW rabbit	BRT/07/145 (non-GLP)	Excipients/Placebo, 60 µL left eye Normal Saline, 60 µL right eye (b) (4) 0.25%, 15 µL left eye 0.25%, 30 µL left eye 0.25%, 60 µL left eye Latanoprost 0.005%, 30 µL left eye Latanoprost 0.005%, 60 µL left eye	No adverse ocular findings based on ophthalmoscopy and histopathology No systemic effects based on clinical signs, body weights, hematology, clinical chemistry, gross pathology and selected organ weight changes The highest dose studied was the NOAEL for both (b) (4) 0.25% and Latanoprost Ophthalmic (b) (4) 0.005%.
14 day NZW rabbits	BRT/08/100 (non-GLP)	Normal Saline, 30 µL/eye QID Excipients/Placebo, 30 µL/eye QID (b) (4) 0.25%, 30 µL/eye QID Latanoprost 0.005%, 30 µL/eye QD Latanoprost 0.005%, 30 µL/eye BID Latanoprost 0.005%, 30 µL/eye TID Latanoprost 0.005%, 30 µL/eye QID	No adverse ocular findings based on ophthalmoscopy (no histopathology) No systemic effects based on clinical signs, body weights, hematology, clinical chemistry, urinalysis, gross pathology and selected organ weight changes Systemic exposure to latanoprost free acid was below the limit of quantitation (5.00 pg/mL) except for 3 females, one each at the BID (Day 14), TID (Day 14), and QID (Day 1 and Day 14) dosing regimens. AUC_{last}: 2.99 to 18.9 pg•hr/mL C_{max}: 5.98 to 13.8 pg/mL Latanoprost free acid was detected in the plasma of these females at only one timepoint (2 or 8 hrs postdose). The highest dose regimen studied was the NOAEL for Latanoprost Ophthalmic (b) (4) 0.005%. The NOAEL for (b) (4) 0.25% was the only dose studied (QID regimen).
30 day NZW rabbit	BRT/09/015 (GLP)	Normal Saline, 30 µL/eye QID Excipients/Placebo, 30 µL/eye QID (b) (4) 0.25%, 30 µL/eye QID Latanoprost 0.005%, 30 µL/eye QD Latanoprost 0.005%, 30 µL/eye BID Latanoprost 0.005%, 30 µL/eye QID	No adverse ocular findings based on ophthalmoscopy and histopathology; conjunctival redness (score 2) at Week 5 in one male at the Latanoprost Ophthalmic (b) (4) 0.005% high dose No systemic effects based on clinical signs, body weights, hematology, clinical chemistry, urinalysis, gross pathology, selected organ weight changes, and histopathology

			Systemic exposure to latanoprost free acid was below the limit of quantitation (50.3 pg/mL) except for 5 males (2 mid dose and 3 high dose) at the 0.5 hr and 1 hr timepoints on Day 1. $C_{0.5\ hr}$: 89.7-192.8 pg/mL $C_{1\ hr}$: 54.3-59.5 pg/mL The highest dose regimen studied was the NOAEL for Latanoprost Ophthalmic (b) (4) 0 005%. The NOAEL for (b) (4) 0.25% was the only dose studied (QID regimen).

An additional 30-day ocular toxicity study was conducted in beagle dogs. As longer-term studies were conducted, this study is briefly summarized below.

A 30-Day Repeated-Dose Range Finding Ocular Toxicity Study of Latanoprost in Beagle-Dogs with Toxicokinetics Evaluation (Study # BRT/09/026; GLP; Module 4.2.3.2) – Beagle dogs (3/sex/group; 5-6 months old) were treated with Latanoprost Ophthalmic (b) (4) 0.005% (batch # JK82671) QD, BID, or QID or (b) (4) 0.25% QID (batch # JK82612) by daily topical instillation for 30 days. Both eyes were treated with a dose volume of 100 µL/eye per instillation. A placebo/excipients control group and a normal saline control group were included, both treated with 100 µL/eye QID.

Parameters evaluated included clinical signs, body weights, food consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, gross necropsy, organ weights (adrenals, brain, kidneys, liver/gallbladder, pancreas, spleen, testes, ovaries, thymus, and thyroids/parathyroids), and histopathology of the eye and full battery of systemic tissues (both control groups, (b) (4) group, and high-dose latanoprost group). TK was evaluated on Days 1, 14, and 30 for saline control and all groups treated with latanoprost.

Congestion of the sclera and conjunctiva and miosis were observed in all male and females receiving latanoprost. The severity (mild to moderate) of the congestion was dose related. Ophthalmology with a mydriatic agent revealed congestion of the retinal blood vessels in both eyes of animals receiving latanoprost (severity was not specified). This finding was not observed in the 180-day repeated-dose ocular toxicity study (Study # BRT_09_075).

Histopathologically, minimal focal lymphocytic infiltration in nictitating membrane, and minimal congestion of the conjunctiva, sclera, and ciliary process was observed in one or both eyes in all groups evaluated. The incidence and/or severity were comparable across groups. Therefore, these findings were considered incidental findings. No test article-related effects were observed in the systemic tissues.

Study title: A 180-Day Repeated-Dose Ocular Toxicity Study of Latanoprost Ophthalmic (b) (4) in Beagle Dogs with Toxicokinetic Evaluation

Study no.:	BRT_09_075
Study report location:	EDR Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11-27-09
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Latanoprost Ophthalmic (b) (4) 0.005% w/v , 2.5 ml (microemulsion), batch # JK82671, 102.5 % pure **Note:** The Certificate of Analysis (CoA) has a manufacturing date of 11-2008 and expiration date of 10-2010. The CoA was signed on 1-23-09. See comments below under "Dosing Solution Analysis". (b) (4) ((b) (4) Solution, 0.25%w/v, batch # JK82612, 96.86% pure **Note:** The CoA has a manufacturing date of 11-8-2008. The CoA date was 11-29-08. See comments below under "Dosing Solution Analysis".

Key Study Findings

- Mild lacrimation and mild to moderate scleral congestion were observed in all groups, which subsequently recovered during the reversal period. The incidence and severity of scleral congestion was higher in the latanoprost-treated groups.
- Mild to moderate miosis was observed in all latanoprost-treated dogs during the dosing period. This finding was considered related to latanoprost pharmacological activity.
- No detectable systemic exposure to latanoprost acid was observed on Days 1 and 90. On Day 180, the systemic exposure was low but measurable (mean C_{max} and AUC_{0-t} of 0.30 µg/mL and 0.051 µg•hr/mL).
- The applicant selected the latanoprost high dose of 0.005% QID as the NOAEL. However, since a higher incidence/severity of scleral congestion was observed in all latanoprost-treated groups, there was no NOAEL in this study.

Methods

Doses:	G1: Saline control , QID G2: Vehicle (Latanoprost Ophthalmic (b) (4) Placebo) control, QID G3: (b) (4) 0.25%, QID G4: Latanoprost 0.005%, QD G5: Latanoprost 0.005%, BID G6: Latanoprost 0.005%, QID
Frequency of dosing:	Daily to both eyes for 182 days; 30 min interval between multiple doses
Route of administration:	Topical instillation into the conjunctival sac
Dose volume:	100 µL/eye/time point
Formulation/Vehicle:	Test articles were provided ready to use.
Species/Strain:	Beagle dogs
Number/Sex/Group:	6/sex/dose in groups G1, G2, G3, and G6; 4/sex/dose in groups G4 and G5 2/sex/dose in groups G1, G2, G3, and G6 were kept for a 30-day recovery period
Age:	6-8 months old
Weight:	9.43-9.77 kg for males; 9.82-10.13 kg for females
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None with an impact in the interpretation of the data

Observations and Results

Mortality (Daily) - None

Clinical Signs (Daily; detailed observations weekly; eye irritation by Draize scoring) - Mild lacrimation and mild to moderate scleral congestion were observed in all groups, which subsequently recovered during the reversal period (Table 9). The incidence and severity of scleral congestion was higher and dose-dependent in the latanoprost-dosed groups. Scleral congestion was most commonly observed at the high-dose from Week 8 onward and at later time points in all other groups. This finding was present at the daily predose observation.

Mild lacrimation was observed sporadically in one group G1 (saline) male on Week 8 only, two group G2 (vehicle) males on Weeks 20 and 21 in one male and Weeks 20-24 in the second male, and two group G6 (latanoprost QID) males on Weeks 5 and 12 in one male and Weeks 12 and 13 in the second male. In females, one group G1 (saline control) and one group G6 (latanoprost QID) animal showed lacrimation throughout the dosing period starting on Week 13 and Week 7, respectively.

All latanoprost-dosed groups showed mild to moderate miosis during the dosing period after instillation of latanoprost at all timepoints due to latanoprost pharmacological effect. This effect was not present at the daily predose observation.

No clinical signs were found at the end of the reversal period indicating complete recovery after dose cessation.

Table 9: Incidence of Lacrimation, Miosis, and Scleral Congestion in Dogs – 180 Repeated-Dose Ocular Toxicity Study

Males

Clinical Signs		Group and Dose (Total Occurrence/Number of Animals)					
		1, Normal Saline, 100µLx4 times/eye/day	2, Placebo , 100µLx4 times/eye/day	3, (b) (4) (b) (4) 100µLx4 times/eye/day	4, Latanoprost, 100µLx1 time/eye/day	5, Latanoprost, 100µLx2 times/eye/day	6, Latanoprost, 100µLx4 times/eye/day
Number of Animals / Group		6	6	6	4	4	6
Number of Animals Observed		6	6	6	4	4	6
Lacrimation	+	2/1	72/2	NA	NA	NA	19/2
Miosis	+	NA	NA	NA	24/4	28/4	12/6
	++				704/4	700/4	1050/6
Scleral congestion	+	567/3	441/5	391/4	694/4	736/4	1224/6
	++	147/1	NA	NA	196/4	220/4	324/6

Females

Clinical Signs		Group and Dose (Total Occurrence/Number of Animals)					
		1, Normal Saline, 100µLx4 times/eye/day	2, Placebo , 100µLx4 times/eye/day	3, (b) (4) (b) (4) 100µLx4 times/eye/day	4, Latanoprost, 100µLx1 time/eye/day	5, Latanoprost, 100µLx2 times/eye/day	6, Latanoprost, 100µLx4 times/eye/day
Number of Animals / Group		6	6	6	4	4	6
Number of Animals Observed		6	6	6	4	4	6
Lacrimation	+	278/1	152/1	3/1	1/1	2/2	298/2
	++	NA	NA	NA	NA	NA	1/1
Miosis	+	NA	NA	NA	28/4	16/4	NA
	++				700/4	712/4	1092/6
Scleral congestion	+	280/2	335/6	340/3	597/4	682/4	1143/6
	++	NA	NA	NA	264/4	276/4	517/6

+ Mild; ++ Moderate

Body Weights (Day 1 and once weekly thereafter) – No test article-related effects

Feed Consumption (Daily) – Dogs were offered approximately 300 g of food daily and left over quantity was measured on the next day. No food left over was found in any dose group throughout the study. Therefore, the data showed the same value across groups for the mean data (2100 g/dog/week) as well as individual animal listings (300 g/dog/day) at all timepoints.

Ophthalmoscopy (Before initiation of dosing, towards the end of dosing on Day 176 [Week 26], and during the recovery period on Day 205 [Week 30]; the description indicates that both eyes were examined with a hand-held ophthalmoscope and the cornea, iris, lens, conjunctiva, lacrimation, chemosis, sclera, fundus and pupillary reaction to light were evaluated) – Findings on Day 176 included scleral congestion (grade 1) and lacrimation. Only two gradings were used for the sclera: 0 = normal and 1= any change of surface or color above normal. Scleral congestion was noted in all latanoprost-treated animals. Three males and 2 females, 4 males and 1 female, and 3 males and 3 females from groups G1 (saline), G2 (vehicle) and G3 (b) (4), respectively, showed scleral congestion during ophthalmoscopy without mydriatic agent on Day 176. Lacrimation was observed in one male and one female of group G1 and one female from group G6 (latanoprost 0.005% QID) during ophthalmoscopy without mydriatic agent on Day 176. These changes recovered by the end of the recovery period.

No pupillary reaction to light was noted and the retina was normal when ophthalmoscopy was carried out with mydriatic agent predose and on Day 86 (Week 13), Day 176 (Week 26) or Day 205 (Week 30) in all dose groups (presumed due to mydriasis). No pupillary reaction to light was noted due to latanoprost-induced miosis when ophthalmoscopy was carried out without mydriatic agent in groups G4, G5 and G6.

ECG (Before initiation of dosing, Day 171 and Day 205) – No test article-related effects

Hematology/coagulation (Before initiation of dosing, Day 86 of dosing, Day 176 and Day 205) – No test article-related effects

Clinical Chemistry (Before initiation of dosing, Day 86 of dosing, Day 176 and Day 205) – On Day 176, one latanoprost high-dose female (#652) showed high levels of ALT, AST, and CK (8.9-11-fold the mean value in group G1) and decreased phosphorous (2.2-fold the mean value observed in group G1). Given the only incidence, and lack of a microscopic correlate, a relationship to latanoprost treatment is unclear.

Urinalysis (Before initiation of dosing, Day 86 of dosing, Day 176 and Day 205) – No test article-related effects

Gross Pathology (End of dosing and recovery periods) – No test article-related effects

Organ Weights (Adrenals, brain, epididymides, heart, kidneys, liver with gall bladder, lungs with main stem bronchi, spleen, testes, ovaries, thymus, thyroids with parathyroid, prostate, pituitary and uterus with cervix; paired organs were weighed together) – No test article-related effects

Histopathology (Microscopic examination of the eye balls, optic nerve and adnexal tissues [cornea, sclera, ciliary processes, iris, retina, lens and nictitating membrane were evaluated separately], and standard battery of systemic tissues from G1, G2, G3, and G6)

Adequate Battery - Yes

Peer Review – Thymus, liver, kidneys, eye, lacrimal gland, nictitating membrane and conjunctiva only

Histological Findings - Minimal focal lymphocytic infiltration in lacrimal glands, nictitating membrane, and conjunctiva was observed in all groups evaluated. The incidence and/or severity were comparable across groups. These were considered incidental findings. No test article-related effects were observed in the systemic tissues.

Bone marrow was collected but not evaluated as no effects were observed in hematology parameters and histopathology of bone marrow from sternum/femur.

Toxicokinetics (Groups G1, G4, G5 and G6 on Days 1 and 90 at 0 [before first instillation], 0.5, 1, 2, 4, 8 and 24 hours post-last instillation. Additional blood samples were collected at 5, 10 and 20 minutes post-last instillation from Group G6 [from males on Day 106 and from females on Day 103]. On Day 180, blood samples were collected at 0 [before dosing], 5, 10, and 20 minutes and 0.5, 1, 2 and 4 hours post-last instillation.) - Daily ocular administration of Latanoprost Ophthalmic [redacted] (b) (4) 0.005%, up to 4 instillations per day, resulted in no or negligible systemic exposure to latanoprost free acid on Days 1 and 90. When observed, mean levels (13.8-48.3 pg/mL) were below the lower limit of quantification of 50.3 pg/mL. On Day 180, the systemic exposure was low but measurable (Table 10).

Table 10: Mean Toxicokinetic Parameters of Latanoprost after Ocular Administration of Latanoprost Ophthalmic (b) (4) 0.005% to Dogs (Day 180)

Group and Dose (µg/kg/day)	4		5		6	
	0.17	0.20	0.36	0.40	0.69	0.87
	Male	Female	Male	Female	Male	Female
C_{max} (µg/mL)	0.21	0.23	0.22	0.18	0.36	0.26
AUC_{0-t} (µg·hr/mL)	0.039	0.051	0.035	0.027	0.064	0.038
AUC_{0-inf} (µg·hr/mL)	0.062	0.081	0.066	0.255	0.091	0.155
T_{max} (hr)	0.104	0.145	0.083	0.083	0.083	0.083

Dosing Solution Analysis – The Latanoprost Ophthalmic (b) (4) 0.005% and (b) (4) 0.25% solution were provided ready to use by the applicant. According to the CoA for Latanoprost Ophthalmic (b) (4) 0.005%, the dosing solution was manufactured one year prior to the date of study initiation. Stability data submitted with the NDA (Section 3.2.P.8.3) showed Latanoprost Ophthalmic (b) (4) 0.005% was stable at 25°C/40% RH, 2-8°C, and 40°C/NMT 25% RH when evaluated for up to 36 months, 12 months, and 6 months, respectively. The storage conditions in the study protocol is mentioned at 2-25°C. Therefore, the data support the stability of the test article under the conditions of the study.

Similarly, (b) (4) ((b) (4) Solution, 0.25%w/v was manufactured one year prior to the date of study initiation. The technical information from (b) (4) states that (b) (4) is stable for at least 24 months if stored in the unopened original containers at room temperature (max. 25°C).

Study title: A 180-Day Repeated Dose-Ocular Toxicity Study of Lantanoprost in New Zealand White Rabbits with Toxicokinetic Evaluation

Study no.: BRT/09/038
Study report location: EDR Module 4.2.3.2
Conducting laboratory and location: Biological Research Toxicology Sun Pharma Advanced Research Company Limited, Tandalja, Vadodara – 390 020, India
Date of study initiation: 5-12-09
GLP compliance: Yes
QA statement: Yes

[1] http://www.pharma-ingredients.(b) (4)com/Statements/Technical%20Informations/EN/Pharma%20Solutions/03_030748e_(b) (4)2015.pdf

Drug, lot #, and % purity: Latanoprost Ophthalmic (b) (4) 0.005% w/v , 2.5 ml (microemulsion), batch # JK82671, 102.5 % pure

(b) (4) ((b) (4) Solution, 0.25%w/v, batch # JK82612, 96.86% pure

Note: The CoA for Latanoprost Ophthalmic (b) (4) 0.005% has a manufacturing date of 11-2008 and expiration date of 10-2010. The CoA was signed on 1-23-09. The CoA for (b) (4) has a manufacturing date of 11-8-2008. The CoA date was 11-29-08. These are the same batches and CoA reported under Study # BRT_09_075 above.

Key Study Findings

- Mild lacrimation and redness in the conjunctiva were observed at the latanoprost high dose (Latanoprost 0.005%, QID). These findings were not present in recovery animals.
- Low systemic exposure to latanoprost acid was observed at all latanoprost doses. On Day 178, the mean C_{max} was 75.1 and 23.7 pg/mL for males and females, respectively; the mean AUC_{0-t} was 45.2 and 22.1 pg•hr/mL, respectively.
- The applicant selected the latanoprost mid-dose of 0.005% BID as the ocular NOAEL and the latanoprost high-dose of 0.005% QID as the NOAEL for systemic toxicity. This reviewer concurs.

Methods

Doses: G1: Saline control , QID
G2: Vehicle (Latanoprost Ophthalmic (b) (4) Placebo) control, QID
G3: (b) (4) 0.25%, QID
G4: Latanoprost 0.005%, QD
G5: Latanoprost 0.005%, BID
G6: Latanoprost 0.005%, QID
G7: Saline control, QID reversal
G8: Vehicle control, QID reversal
G9: (b) (4) 0.25%, QID reversal
G10: Latanoprost 0.005%, QID reversal

Frequency of dosing: Daily to both eyes for 180 days; 30 min interval between multiple doses

Route of administration:	Topical instillation by pulling the lower eyelid
Dose volume:	30 µL/eye/time point
Formulation/Vehicle:	Test articles were provided ready to use.
Species/Strain:	New Zealand White (NZB) rabbits
Number/Sex/Group:	6/sex/dose in groups G1 to G6; 4/sex/dose in G4 and G5; 2/sex/dose in groups G7 to G10
Age:	9 months old
Weight:	2.31-2.71 kg in males; 2.49-2.94 kg for females
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None with an impact in the interpretation of the data

Observations and Results

Mortality (Daily) - None

Clinical Signs (Daily; detailed observations weekly) – Mild lacrimation was noted in daily clinical observations in one male (#608) of group G10 (latanoprost 0.005% QID) from Day 34 to 147 and from Day 175 to 191 (reversed during the recovery period). Mild redness in the conjunctiva was observed in two group G6 (latanoprost 0.005% QID) males from day 111 to 130 (#603) and from day 77 to 82 (#605) in daily observations as well as in weekly detailed observations using Draize scoring.

Mild redness in the conjunctiva was also observed in 3 females in group G6 (#654 from day 96 to 180, # 655 from day 51 to 54, and # 656 from day 43 to 46, 56 to 65, and 69 to 180) in daily observations. The finding was reported in two of these females (#654 and #656) in weekly detailed observations using Draize scoring. These findings were not present in recovery females (# 657 and # 658).

Body Weights (Day 1 and once weekly thereafter) – No test article-related effects

Ophthalmoscopy (Before initiation of dosing, towards the end of dosing on Day 175 and during the recovery period on Day 206; the description indicated that both eyes were examined with a hand-held ophthalmoscope and the cornea, iris, lens, conjunctivae, lacrimation, chemosis, sclera, fundus and pupillary reaction to light were evaluated) – Mild lacrimation in both eyes was observed in one male (#608) in group G10 (latanoprost 0.005% QID) during ophthalmoscopy on Days 85 and 175, while no lacrimation was noted on Day 206 which indicated recovery. Some conjunctival blood vessels were hyperemic in one female on Day 85 (#656) and two females (#654 and #656) on Day 175 of group G6 (latanoprost 0.005% QID). On Day 206, these findings were not present in recovery females (#657 and # 658).

No abnormal pupil reaction to light was noted and the retina was found normal when ophthalmoscopy was carried out with mydriatic agent on Day 85, 175 and Day 206 in all study groups.

Hematology/coagulation (Before initiation of dosing, on Day 85, Day 175, and Day 206) – No test article-related effects

Clinical Chemistry (Before initiation of dosing, on Day 85, Day 175, and Day 206) – No test article-related effects

Urinalysis (Before initiation of dosing, on Day 85, Day 175, and Day 206) – Some animals showed levels of urobilinogen (2.0 E.U./dL) above normal range (0.2-1 E.U./dL). These included male #307 ((b) (4) 0.25%, QID), male #505 (latanoprost 0.005%, BID), and female #455 (latanoprost 0.005%, QD) on Day 175, and female # 657 (latanoprost 0.005% QID) on Day 206 (recovery). Male #307 was evaluated during recovery; levels returned to normal. Based on the lack of effects in RBC, bilirubin, renal and liver parameters, this finding does not appear related to the test article.

Gross Pathology (At the end of the dosing and recovery periods) – No test article-related effects

Organ Weights (adrenal glands, brain, heart, kidneys, liver with gall bladder, spleen, testes, ovaries, thymus and thyroids with parathyroids; paired organs were weighed together) – No test article-related effects

Histopathology (Microscopic examination of the eye balls, optic nerve and adnexal tissues [cornea, sclera, ciliary processes, iris, retina, lens and nictitating membrane were evaluated separately], and standard battery of systemic tissues from groups G1, G2, G3, and G6; tissues from groups G4 and G5 when abnormal findings were observed in G6)

Adequate Battery - Yes

Peer Review – Liver, kidneys, brain, right eye and left eye only

Histological Findings - Minimal focal lymphocytic infiltration was observed in the lacrimal glands and nictitating membrane in all groups evaluated. The incidence and/or severity were comparable across groups. These were considered incidental findings.

No test article-related effects were observed in the systemic tissues. Some findings showed higher incidence in placebo, (b) (4) and/or latanoprost high-dose groups compared to saline controls (Table 11). Except for granulomas, these findings were not observed in systemic route toxicity studies. Therefore, they are probably unrelated to the respective treatments.

Granulomas of minimal severity were observed in the liver in the rat 3-month IV toxicity study after administration of (b) (4) (Study # 87-H-82) at all doses evaluated (250-1000 mg/kg). Based on the dose difference, 250 mg/kg vs. an

estimate of 0.25 mg/kg after topical ocular administration (assuming 100% absorption), it is difficult to definitely attribute the finding of microgranulomas to the presence of (b) (4) in all these groups.

Table 11: Microscopic Findings in Systemic Tissues in the 180-Day Repeated-dose Ocular Toxicity Study in Rabbits (Males; Females)

Finding	Saline	Placebo	(b) (4)	Latanoprost (high dose)
Liver microgranuloma (minimal)	1/6; 0/6	3/6; 3/6	2/6; 1/6	2/6; 2/6
Brain cortex gliosis				
minimal	0/6; 0/6	2/6; 0/6	2/6; 2/6	1/6; 0/6
mild	--	--	--	1/6; 0/6
Pituitary cyst				
minimal	2/5; 1/4	2/6; 1/5	2/6; 2/6	4/6; 3/6
mild	---	1/6; 0/5	0/6; 1/6	---
Oligospermia (minimal)	1/6	1/6	---	3/6

--No abnormality detected

Bone marrow was collected but not evaluated as no effects were observed in hematology parameters and histopathology of bone marrow from sternum/femur.

Toxicokinetics (Groups 1, 4, 5 and 6 on Days 1, 90 and 178 of dosing at 0 (just before dosing), 0.5, 1, 2, 4, 8 and 24 hours post last instillation) – The plasma concentrations of latanoprost free acid were low in all latanoprost-dose groups during the 180-day study period (Table 12). The highest plasma C_{max} and AUC_{0-t} were observed in the high-dose group on Day 90. The mean concentrations were, in many samples, below the LLOQ of 50.3 pg/mL. Plasma concentrations were only detectable in the 0.5 hour timepoint, except for females given latanoprost 0.005% BID on Day 1 (detected up to 4 hours post last instillation), males given latanoprost 0.005% QID on Day 90 (detected up to 2 hrs post last instillation), and male and females given latanoprost 0.005% QID on Day 178 (detected up to 1 hr post last instillation). Given the variability in the data, determination of accumulation was difficult.

Table 12: Mean TK Values on Day 1, 90, and 178 following Daily Ocular Instillation of Latanoprost Ophthalmic (b) (4) 0.005% to NZW Rabbits

Dose (µg/animal/day)		1.5		3.0		6.0	
		Male	Female	Male	Female	Male	Female
C_{max} (pg/mL)	Day 1	0.00	0.00	19.00	19.77	58.57	0.00
	Day 90	30.10	37.57	70.50	30.43	426.87	120.67
	Day 178	0.00	0.00	308.03	63.30	75.13	23.67
AUC_{0-t} (pg·hr/mL)	Day 1	0.000	0.000	4.750	55.683	14.642	0.00
	Day 90	7.525	9.392	17.625	7.608	257.308	30.167
	Day 178	0.000	0.000	77.008	15.825	45.233	22.108
AUC_{0-inf} (pg·hr/mL)	Day 1	*	*	*	*	*	*
	Day 90	*	*	*	*	281.241	*
	Day 178	*	*	*	*	*	*
T_{max} (hr)	Day 1	*	*	0.50	4.00	0.50	*
	Day 90	0.50	0.50	0.50	0.50	0.50	0.50
	Day 178	*	*	0.50	0.50	0.50	0.50

*: value not estimable.

Dosing Solution Analysis - See comments above under Study # BRT_09_075.

Systemic Route Studies:

Repeated-dose systemic toxicity studies of 2-week, 4-week and 3-month duration in rats and 4-week duration in dogs conducted with (b) (4) were previously reviewed under the initial IND. The main findings are summarized in Table 13.

Table 13: Summary of Subchronic Systemic Route Toxicity Studies Conducted with (b) (4)

Study	Study #	Dose (mg/kg/day)	Results
2-week IV rats (Chbb:THOM)	52K (GLP)- (b) (4)	0 (10% sorbitol), 25, 75 and 200	Subcellular fat storage in the spleen at 200 mg/kg NOAEL = 75 mg/kg
4-week IV rats (Chbb:THOM)	53K (GLP)- (b) (4)	0 (10% sorbitol), 25, 75 and 200	Lipid accumulation in the sinus endothelial cells of the spleen at 200 mg/kg; not reversible after a 4-week recovery period Slight focal lipid storage in the spleen in one animal at 75 mg/kg NOAEL = 25 mg/kg
30-day PO rats (Wistar)	BRT-08-091 (non-GLP)- SPARC	0 (saline), 500, 1000, and 2000 (gavage)	NOAEL = 2000 mg/kg
3-month IV rats (Chbb:THOM)	87-H-82 (GLP) ((b) (4)	0 (sorbitol), 250, 500, 750 and 1000* *The 1000 mg/kg dose was discontinued as all animals died of pulmonary edema; a replacement group at 750 mg/kg was added.	Dose-dependent deposits of granular brown lipophilic pigments in the sinus endothelial cells of the spleen and liver in all (b) (4) treated groups Dose-dependent increase in number and size of small

			granulomas in the liver; granulomas contained lipid drops containing brown pigment granules; granulomas were composed of various cell types including lymphocytes, eosinophilic granulocytes, mesenchymal cells Deposits of brown lipid-positive pigment were still present in the liver and spleen after the 6-week recovery period (recovery only evaluated for control and high dose group). Authors believe lipid drops (brown pigment) possibly represent denaturation products of stearic acid. No NOAEL
4-week IV dog (beagle)	70D0114/8605 (GLP) - (b) (4)	(b) (4) 0 (10% sorbitol), 5, 25, 50, and 100 (b) (4) EL (positive control): EL 5, and 25	Pruritus and erythema at ≥50 mg/kg; wheals at 100 mg/kg (b) (4) (5 and 25 mg/kg): pruritus, erythema, generalized wheal formation, somnolence, emesis, staggering, spontaneous defecation, and mild apathy Symptoms generally resolved within 15-60 min ((b) (4) or 30-60 min (b) (4) No increased incidence of fatty drops or pigment deposits in liver, spleen or lymph nodes as compared to controls No NOAEL as 2 females at 5 mg/kg collapsed briefly after the 6th administration **Note:** This reviewer believes the NOAEL could be 25 mg/kg as higher dose animals did not collapse. In addition, there were no signs of allergic reaction at the low dose. Therefore, the finding at the low dose does not appear directly related to (b) (4)
4-week PO dog (beagle)	910866 (GLP) (b) (4)	0 (blank gelatin capsules), 258, 515, 1030	Diarrhea in all (b) (4) dose groups (non-dose dependent) and vomiting at the high dose (1st week only) NOAEL = 1030 mg/kg

The applicant conducted an additional repeated-dose oral toxicity study of 6-month duration with (b) (4)

Study title: A 180-Day Repeated-Dose Oral Toxicity Study of (b) (4) in Wistar Rats

Study no.:	BRT/09/023
Study report location:	EDR Module 4.2.3.2
Conducting laboratory and location:	Biological Research Toxicology Sun Pharma Advanced Research Company Limited, Tandalja, Vadodara – 390 020, India
Date of study initiation:	3-10-09
GLP compliance:	Yes (OECD)
QA statement:	Yes
Drug, lot #, and % purity:	(b) (4) batch # 27473868E0, complies with PhEur/IHS

Key Study Findings

(b) (4) caused no adverse effects at daily oral doses up to 1000 mg/kg.

Methods

Doses:	G1:Normal saline G2: Low dose (250 mg/kg/day), G3: Mid dose (500 mg/kg/day) G4: High dose (1000 mg/kg/day) G5: Normal saline Reversal G6: Low dose reversal (250 mg/kg/day) G7: Mid dose reversal (500 mg/kg/day) G8: High dose reversal (1000 mg/kg/day).
Frequency of dosing:	Once daily for 180 days
Route of administration:	Oral intubate needle (gavage)
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.9% saline
Species/Strain:	Wistar rats
Number/Sex/Group:	20/sex/group in groups G1 to G4; 10 sex/group for reversal groups G5 to G8 (34-36 recovery period)
Age:	7-8 weeks
Weight:	211-223 g for males; 162-167 g for females
Satellite groups:	None
Unique study design:	2 animals/sex/cage were housed during the dosing period and recovery period (p. 25).
Deviation from study protocol:	None with an impact on the interpretation of the data

Observations and Results

Mortality (Twice daily) – The following animals were found dead during the study (between Days 3 to 149). High-dose (Group G4) female # 466 was sacrificed moribund due to an injury in the median side of left shoulder considered due to probing (dosing) injury.

Table 14: Mortalities Observed in the 180-Day Repeated-Dose Oral Toxicity Study of (b) (4) in Rats

Group	Male	Female
G2: 250 mg/kg	#209, #212, and #219	#253
G3: 500 mg/kg	#310, #312 and #316	
G4: 1000 mg/kg	#416 and #419	#451, #462 and #466
G6: Reversal 250 mg/kg	#223 and #224	
G7: Reversal 500 mg/kg		#378
G8: Reversal 1000 mg/kg	#428	#478

In most of these animals (see exceptions below), gross findings observed included wetness and frothy discharge around mouth and nostrils, frothy discharge after cutting open he trachea and lung, encapsulation of test article in body cavity (below right shoulder due to probing/dosing injury; within thoracic cavity) along with fluid, lung lobes red in color, lung with congested appearance, and/or infection due to dosing injury/probing injury. All these findings were suggestive of death due to an intubation error.

The organs in female # 451 were semiautolytic; the cause of death for this animal could not be ascertained. The cause of death of male # 312 was attributed to a head injury (not clear to this reviewer how this happened).

Clinical Signs (Twice daily; once weekly for detailed observations) – No test article-related findings

Body Weights (Weekly) – No test article-related effects

Feed Consumption (Weekly) – No test article-related effects

> **Note:** The value took into account the number of animals in the cage. This is considered a study limitation as animals should have been housed individually if food consumption was to be conducted. However, based on the lack of an effect on body weights, this limitation is not considered to affect the interpretation of the data.

Ophthalmoscopy (Before initiation of dosing in all main group animals and at Week 25 for G1 control and G4 high-dose main groups; the description indicated that both eyes were examined with a hand-held ophthalmoscope and the cornea, iris, lens, conjunctivae, lacrimation, chemosis, sclera, fundus and pupil reaction to light were evaluated) – No test article-related effects

Hematology/coagulation (Week 13, Week 26, and Week 29-30 [recovery period] for main group animals; first 10 animals/sex/group prothrombin time in the remaining animals/sex/group) – At Week 30 (recovery period), there was a trend toward increased mean monocyte % values in males and females at all (b) (4) doses (Table 15). This finding was significantly different only in high-dose males. Because a similar finding was not observed during treatment, this finding seems to be unrelated to the test article.

Table 15: Changes in Monocyte% Values at Week 30 (Recovery) in Rats after Oral Treatment with (b) (4)

		Group (Dose)							
		5 (0mg/kg/day)		6 (250mg/kg/day)		7 (500mg/kg/day)		8 (1000mg/kg/day)	
		M	F	M	F	M	F	M	F
Monocyte (%)	Mean	2.07	2.51	2.55	3.17	2.74	4.77	3.40 ↑	4.08
	SD	0.704	0.917	0.763	1.071	0.744	5.394	0.876	0.893
	N	10	10	8	10	10	9	9	9

↑: Significantly higher than respective control ($p<0.05$) using Dunnett's test

Clinical Chemistry (Week 13, Week 26, and Week 29-30 [recovery period] for main group animals) – No test article related effects

Urinalysis (Week 13, Week 26, and Week 29-30 [recovery period] for main group animals)- No test article-related effects

Gross Pathology (All animals at the end of dosing and recovery periods; includes animals found dead during the study) – No test article-related findings

Note: Under the findings section of the full study report, frothy discharge around mouth and nostril, frothy discharge in trachea and lung, encapsulation of test article in body cavity along with fluid) were reported in animals found dead including controls. However, the summary tables and individual animal listings showed that no mortalities or abnormalities were observed in control animals.

Organ Weights (All surviving animals; adrenals, brain, epididymides, heart, kidneys, liver, lungs with main stem bronchi, prostate, spleen, testes, thymus, ovaries with fallopian tube, and uterus; paired organs were weighed together) – No test article-related effects

Histopathology (All tissues from groups G1 and G4; surviving animals only) -

Adequate Battery – Yes

Note: Bone marrow smears were prepared from femur bone but not evaluated as no test article-related findings were observed in hematology and histopathology of the bone marrow of femur and sternum of group G4.

Peer Review – Yes (liver, kidney, and adrenal glands only)

Histological Findings – No test article-related findings

Toxicokinetics – TK was not evaluated because (b) (4) is a complex blend of several families of ethoxylated 12-hydroxystearic acid derivatives, and therefore, it is not possible to label or detect it as an intact product.

Dosing Solution Analysis - Test article solution was prepared at fifteen days interval. Test article solutions sent on 03-18-09, 06-09-09 and 09-03-09 showed concentration between 103.7% to 108.1% label claim for groups G2, G3, G4, G6, G7 and G8.

7 Genetic Toxicology

Genotoxicity of latanoprost was addressed in the application for Xalatan® (NDA 20-597). Information in the FDA approved label indicates that latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed *in vitro* with human lymphocytes. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative.

No substantial changes are recommended for this section of the proposed label, except that we recommend moving the genetic toxicity information below the carcinogenicity data to be consistent with agency-wide format.

(b) (4) was not genotoxic in the in the Ames test, *in vitro* mammalian chromosomal aberration assay in V79 Chinese Hamster lung fibroblasts, in the *in vitro* mammalian cell (V79) HPRT gene mutation assay, and in the *in vivo* mouse micronucleus assay (single IV dose up to 2150 mg/kg). The concentrations used in each assay are shown in Table 16. These studies were previously reviewed by Dr. Theresa Allio under IND 102842.

Table 16: Genotoxicity Studies Conducted with (b) (4)

Type of Study (Study/Report No.)	Species and Strain	Concentrations (µg/mL or plate) / Doses (mg/kg)	GLP
In vitro			
Bacterial Reverse Mutation Test (*AFP 124*)	*S. typhimurium* strains : TA 98, TA1537, TA100, TA1535, and TA102	15.8, 50, 158, 500, 1580, 5000 (- S-9); 5, 15.8, 50, 158, 500, 1580, 5000 (+ S-9)	Yes
Mutagenicity Study of (b) (4) in Mammalian Cells (V79) in the in vitro Gene Mutation Assay (*9673/96*)	Chinese hamster lung fibroblasts (V79, genetic marker HPRT)	Preliminary trial: 1.3, 6.5, 13, 65, 130, 650, 1300 (± S-9). Main study: 37.5, 75, 150, 300, 600, 800 (- S-9); 125, 250, 500, 1000, 1500 (+ S-9)	Yes
Mammalian Cytogenetic Test in V79 Chinese Hamster Fibroblasts (Chromosome Analysis) (*907380*)	Chinese hamster lung fibroblasts (V79 A2)	10, 32, 100, 320, and 500 (-S-9); 50, 150, 500, 1500, and 5000 (+ S-9)	Yes
In vivo			
Mouse Micronucleus Test (*907402*)	NMRI mice	1st study: 2150 2nd study: 1000, 1470, 2150	Yes

8 Carcinogenicity

Carcinogenicity of latanoprost was addressed in the application for Xalatan® (NDA 20-597). Information in the FDA approved label indicates that latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 µg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively. The applicant is proposing to use the information in the approved Xalatan® label for Latanoprost Ophthalmic (b) (4) 0.005%.

No changes are recommended for this section of the proposed label.

Carcinogenicity studies were not conducted with (b) (4) The applicant listed that following facts as supportive evidence for low risk of a carcinogenic potential for (b) (4):

- There are no structural or pharmacological alerts for (b) (4) to any known class of carcinogens.
- The available data from genotoxicity testing and from repeated-dose toxicity studies have not shown any mutagenic, clastogenic, or proliferative effects.

Given the topical ocular route of administration and the single drop daily regimen, the systemic exposure to (b) (4) is expected to be minimal. Therefore, the

overall data presented with the current marketing application provide support to conclude there is a low risk for carcinogenicity.

A cursory review of the published information revealed that (b) (4) has been approved in Canada and Argentina in marketed injectable-drug products . The (b) (4) webpage[3] indicates that (b) (4) (under the tradename, (b) (4)) is used for manufacturing (b) (4)

The current applicant also provided the following additional information: "As reported by (b) (4) (b) (4) has been used in an injectable human drug, (b) (4) (b) (4) they are not aware of any excipient-related adverse events from either of these uses."

However, the duration of treatment of these injectable (b) (4) formulations was not specified.

9 Reproductive and Developmental Toxicology

Reproductive and developmental toxicity of latanoprost in all three segments (segment I, II, and III) were evaluated in the application for Xalatan® (NDA 20-597). Information in the FDA approved label indicates that latanoprost has not been found to have any effect on male or female fertility in animal studies. Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. The applicant is proposing to use the information in the approved Xalatan® label for Latanoprost Ophthalmic (b) (4) 0.005%.

Except for the deletion (b) (4) no changes are recommended for this section of the proposed label.

Effects of (b) (4) on reproductive and developmental function were studied in rats and rabbits following IV administration. The studies included a combined study of embryo-fetal development and prenatal and postnatal development study in rats and an embryo-fetal development study in rabbits. These studies were previously reviewed by Dr. Theresa Allio under IND 102842 and the main results are summarized below.

[2] http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=694692&pageID=2
[3] http://www.pharma-ingredients. (b) (4)

In an embryofetal development toxicity study in rabbits there was a significant increase (2.4X) in the number of resorptions at the high (b) (4) dose of 464 mg/kg/day IV administered from gestation days 6 through 18. As a consequence, an increase in post-implantation loss and a decrease in live fetuses were observed at the same dose. In addition, fetal incidences of misaligned sternebrae and total skeletal variations were increased in the high-dose group and were considered statistically significant (4X and 2X over controls, respectively ≤ 0.05). The NOAEL for fetuses was 215 mg/kg; the NOAEL for dams was 464 mg/kg.

In a combined embryotoxicity and pre- and postnatal reproduction toxicity study in rats no external, visceral or skeletal abnormalities at (b) (4) doses of up to 464 mg/kg/day IV when dosing from gestation days 6 through17. Extension of dosing from Day 6 of gestation to Day 21 of lactation did not show adverse effects on prenatal or postnatal development, nor was maternal function significantly affected at doses up to 464 mg/kg/day. The maternal and fetal NOAEL was 464 mg/kg/day.

The exposure margins based on mg/m^2 (systemic exposure of (b) (4) was not evaluated) indicate there is no concern for reproductive or embryofetal effects after topical ocular administration of Latanoprost Ophthalmic (b) (4) 0.005% at the intended clinical dosing regimen (Table 17).

Table 17: Exposure Margins for (b) (4) Induced Embryotoxicity

Species	NOAEL (mg/kg)	NOAEL (mg/m^2)	Exposure Margin*
Rabbits	215	2580	27,892
Rats	≥464	≥2784	≥30,097

*Human dose of one drop of 0.25% = 0.075 mg/eye (30 µL drop) = 0.15 mg/day (both eyes treated) = 0.0025 mg/kg (60 kg body weight) = 0.0925 mg/m^2

10 Special Toxicology Studies

(b) (4) was evaluated for the potential for skin sensitization, ocular and dermal irritancy, and hemolysis. These studies were previously reviewed by Dr. Theresa Allio under IND 102842 and the results are briefly summarized below

In guinea pig maximization sensitization and open epicutaneous tests, (b) (4) (b) (4) showed skin sensitizing activity at concentrations of 5% and 1-30%, respectively. (b) (4) (0.001-100 mg/mL) did not cause hemolysis *in vitro* in rabbit erythrocytes. In rabbits following single topical ocular administration of 61 mg undiluted (b) (4), transient and slight to moderate conjunctival redness, chemosis and discharge were observed. (b) (4) (0.5 g) showed slight dermal irritation when applied to intact rabbit skin.

The applicant indicated that (b) (4) does not absorb UV or visible light in the range of 350 to 700 nm, therefore, no phototoxicity study was conducted.

11 Integrated Summary and Safety Evaluation

This NDA seeks approval for SPARC Latanoprost Ophthalmic (b) (4) 0.005%, which is proposed for the same dosage (1 drop or 1.5 µg) and administration (once daily in the evening) as that of the approved LD Xalatan®, for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

Unlike Xalatan®, this new formulation is benzalkonium chloride free and contains an excipient, (b) (4) that has not been previously approved in an ophthalmic product in the United States.

The activity and safety of latanoprost ophthalmic (b) (4) has been adequately evaluated in extensive animal and *in vitro* studies, as well as in the human data through marketing experience of Xalatan®. For this NDA submission, SPARC is relying on FDA's prior decision of the efficacy and safety of latanoprost, as summarized in the most current labeling (revised August 2012).

SPARC conducted a comparative plasma and ocular tissue distribution study of Latanoprost Ophthalmic (b) (4) and Xalatan®. The main differences in ocular tissue distribution include higher levels of latanoprost in the vitreous, optic nerve, and retina and lower levels in the conjunctiva, iris/ciliary body, and lens observed in Latanoprost Ophthalmic (b) (4) 0.005% compared to Xalatan®. Latanoprost free acid plasma levels were low for both formulations. Plasma AUC was 2.7-fold higher and half-life was longer for Latanoprost Ophthalmic (b) (4) 0.005% compared to Xalatan®, however, C_{max} was reduced (0.80-fold). The observed differences did not translate into differences observed in the general toxicity studies.

In the 180-day ocular toxicity study in dogs, findings included an increased incidence of scleral congestion compared to controls (saline, placebo, and (b) (4) (b) (4) and miosis at all latanoprost doses (QD, BID, and QID). The severity (mild to moderate) of the congestion was dose related. The miosis was an expected pharmacological effect. No clinical signs were found at the end of the non-dosing period indicating complete recovery after dose cessation. An ocular NOAEL was not established in this study. No systemic adverse findings were observed in any of the Latanoprost Ophthalmic (b) (4) 0.005% dose groups or (b) (4) alone arm (0.25% QID).

In the 180-day repeated-dose ocular toxicity study in rabbits, mild lacrimation and redness in the conjunctiva were observed at the latanoprost high dose (Latanoprost Ophthalmic (b) (4) 0.005%, QID). These findings reversed during the recovery period. There were no systemic adverse findings. Given the lack of similar findings in any other treatment group (including the saline, placebo, and (b) (4) control groups), the NOAEL was the mid dose, Latanoprost Ophthalmic (b) (4) 0.005% BID. No ocular or systemic adverse findings were observed in the (b) (4) alone arm (0.25% QID).

Systemic exposure of latanoprost free acid following ocular administration of Latanoprost Ophthalmic (b) (4) 0.005% up to 4x/day was relatively low. In dogs, no or negligible systemic exposure to latanoprost free acid was observed on Days 1 and 90. At 180 days, the mean C_{max} and AUC_{0-t} were ≤0.36 µg/mL and ≤0.064 µg•hr/mL, respectively. In rabbits, the mean concentrations were, in many samples, below the LLOQ of 50.3 pg/mL. The highest plasma C_{max} and AUC_{0-t} were observed in the high-dose group on Day 90 (i.e., ≤427 pg/mL and ≤257 pg•hr/mL, respectively).

Repeated-dose systemic route toxicity studies of 2-week, 4-week, 3-month, and 6-month duration in rats and 4-week duration in dogs conducted with (b) (4) No adverse findings were observed after oral dosing in rats or dogs. The NOAEL was the highest dose used in each study (2000 mg/kg PO in 4-week rat study, 1030 mg/kg PO in 4-week dog study, and 1000 mg/kg PO in 6-month rat study).

In contrast, IV administration to rats resulted in lipid accumulation in the sinus endothelial cells in the liver and spleen. In addition, there was a dose-dependent increase in number and size of small granulomas in the liver (granulomas contained lipid droplets with brown pigment granules). The lipid deposits were still present in the liver and spleen after a recovery period of up to 6 weeks. The NOAEL was 75 mg/kg IV in the 2-week study and 25 mg/kg IV in the 4-week study. There was no NOAEL in the 3-month study (lowest dose was 250 mg/kg IV).

The applicant concluded that the lipid deposits in the reticuloendothelial system (RES) of liver and spleen, as well as the granulomatous cell aggregations in the liver, were of no toxicological concern. The lipid deposits were thought to represent denaturation products of stearic acid. The predominant function of the cells within the RES is phagocytosis of foreign or altered material. The lipid granule-containing cells of the RES were considered as storage phenomena within physiological processes of eliminating foreign substances. Based on the lack of any other toxicity, the reviewer believes the applicant's interpretation of a storage phenomenon is reasonable. However, it is unknown if these stored deposits will remain harmless or can initiate other changes as they were still present after a 6-week recovery period.

Intravenous administration of (b) (4) to beagle dogs resulted in signs of an allergic reaction (pruritus, erythema, wheals) which resolved within 15-60 min postdose. The NOAEL was 25 mg/kg. In a published study conducted by (b) (4) in beagle dogs, (b) (4) led to an anaphylactoid reaction and an increase in the release of plasma histamine. A (b) (4) dose of 25 mg/kg IV (administered 19 times; dosing frequency not specified) was also the NOAEL in this study, as there were no clinical signs or histamine release at this dose. (b) (4), a surfactant known to induce histamine release and an anaphylactoid reaction, showed an increase in plasma histamine 10-fold higher than that of (b) (4)

As noted by the applicant, the anaphylactoid reaction in dogs and the lipid storage in RES cells in rats observed after IV administration might be route and/or species dependent. For example, the 4-week oral toxicity study in dogs showed that

even at doses as high as 1030 mg/kg/day, (b) (4) did not cause any symptoms associated with spontaneous histamine release. In the oral toxicity studies in the rat of 4-week and 180-day duration, there was no toxicity by the oral route, and lipid storage was not observed at doses up to 2000 mg/kg and 1000 mg/kg, respectively. The lack of findings by the oral route of administration could be related to poor oral absorption[4].

The exposure margins for the ocular findings observed in dogs and rabbits are shown in Table 18. The dose volume of 100 µL in the dog is expected to result in more drug spillage over the eyelid margin compared to a dose volume of 30 µL in humans. Thus, the actual exposure margin is expected to be lower. The ocular findings observed in the nonclinical studies were also observed in the clinical trials. According to the Clinical Overview of this marketing application (Section 2.5), the most commonly reported treatment-related adverse events after treatment with Latanoprost Ophthalmic (b) (4) 0.005% were eye pain, ocular hyperemia, conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening. The sensitivity for the occurrence of miosis appears to be species dependent. Its occurrence in human following treatment with latanoprost is not common.

4 (b) (4) Final Review: Committee for Veterinary Medicinal Products; (b) (4) Summary Report (June 2003) – Section 4.3 Literature References of current NDA.

Table 18: Exposure Margins for Ocular Findings Observed in Dogs and Rabbits after Topical Ocular Administration of Latanoprost Ophthalmic (b) (4) 0.005% for 180 Days

Toxicity	Species (Study duration)	NOAEL (%)	NOAEL (total mg/eye)	Exposure Margin (Based on mg/eye[c])
↑incidence and severity (mild to moderate) of scleral congestion Mild to moderate miosis	Dogs (180 days)	<0.005% QD	<0.005[a]	<3.33
Mild lacrimation &redness of the conjunctiva	Rabbits (180 days)	0.005% BID	0.003[b]	2

[a]Dose volume = 100 µL
[b]Dose volume = 30 µL
[c]Human dose: One drop of 0.005% QD per eye: 0.05 mg/mL x 0.030 mL x 1 dose = 0.00150 mg/eye

The safety margins for systemic toxicities observed after IV dosing with (b) (4) are shown in Table 19. Based on the exposure margins, similar findings are unlikely to be observed in the clinic.

Table 19: Exposure Margins for Systemic Findings Observed in Rats and Dogs after IV Dosing with (b) (4)

Toxicity	Species (Study duration)	NOAEL (mg/kg)	NOAEL (mg/m^2)	Exposure Margin (Based on mg/m^2)
Lipid accumulation in sinus of endothelial cells in liver and spleen	Rats (4 weeks)	25	150	1622
Deposits of granular brown lipophilic pigments in the sinus endothelial cells in the liver and spleen ↑ number and size of small granulomas (lipid containing) in the liver	Rats (3 months)	<250	<1500	<16220
Allergic reaction (pruritus, erythema, wheals)	Dogs (4 weeks)	25	500	5400

*Human dose of one drop of 0.25% = 0.075 mg/eye (30 µL drop) = 0.15 mg/day (both eyes treated) = 0.0025 mg/kg (60 kg body weight) = 0.0925 mg/m^2

In an embryofetal development toxicity study in rabbits, there was a significant increase (2.4-fold) in the number of resorptions and post-implantation loss and a decrease in live fetuses at the high (b) (4) dose of 464 mg/kg/day IV. In addition, fetal incidences of misaligned sternebrae and total skeletal variations were increased at this dose. The exposure margins of >27,000X (on a mg/m^2) indicate that there is no concern for reproductive or embryofetal effects after topical ocular administration of (b) (4), 0.25% in Latanoprost Ophthalmic (b) (4) 0.005%, at the intended clinical dosing regimen.

(b) (4) was not genotoxic in the in the Ames test, *in vitro* mammalian chromosomal aberration assay in V79 Chinese Hamster lung fibroblasts, in the *in vitro* mammalian cell (V79) HPRT gene mutation assay, and in the *in vivo* mouse micronucleus assay.

Carcinogenicity studies were not conducted with (b) (4) Given the topical ocular route of administration and the single drop daily regimen, the systemic exposure to (b) (4) is expected to be minimal. The overall data presented with the current marketing application provide support to conclude there is a low risk for carcinogenicity.

In conclusion, the nonclinical studies presented provide adequate safety information to support the intended dosing regimen of Latanoprost Ophthalmic (b) (4) 0.005% in humans. Approval is recommended.

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

/s/

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